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CHRONIC ULCERATIVE COLITIS IN CHILDHOOD

JEAN HOLOWACH, M.D., AND DON L. THURSTON, M.D.
ST. LOUIS, MO.

BETWEEN 1934 and 1953, eighteen children having chronic ulcerative colitis were admitted to the St. Louis Children's Hospital. A review of their courses before, during, and after hospitalization has served to emphasize to us the difficulties associated with treating chronic ulcerative colitis during childhood.

Chronic ulcerative colitis is not common in childhood. During the interval covered by this study there were 68,832 admissions to St. Louis Children's Hospital. Therefore, the case incidence of chronic ulcerative colitis in this institution was 0.026 per cent, or one in 3,823 admissions, which is an exceedingly low figure. Five infantile cases of acute fulminant ulcerative colitis discovered only during necropsy were excluded from the report because of the uncertainty of the relationship between the acute fulminant and the chronic forms of this syndrome. Three of these five cases were newborn infants, one was 6½ months, and another was 14 months old.

Sex, Age of Onset and Duration of Symptoms.—Twelve of the eighteen patients were girls.

Of interest is the early age of onset of symptoms in our patients. The age range was 18 months to 14½ years when the disease began. Thirteen of the eighteen were less than 7½ years of age and seven (38.8 per cent) were less than 3½ years of age.

The duration of symptoms before their first admission to the hospital ranged from five weeks to ten years. Five had had the disease for more than five years. The mean duration of illness prior to admission was three years.

Symptoms and Signs.—The symptoms and signs of chronic ulcerative colitis in childhood do not differ from those in adults except in degree. We agree with the opinion of others that the course in children is peculiarly stormy and malignant.

Three of the eighteen patients suffered adiarrheal melena as the first manifestation of the disease. One had two attacks of asymptomatic melena, one ten months and the other five months before diarrhea began; another for a three-year prodromal period had attacks of melena with cramps, biannually. These attacks lasted one to four days. The third had irregular periods of melena for one and one-half years

From the Department of Pediatrics, Washington University School of Medicine.

before the full-blown picture of the disease appeared.

Two patients showed an allergic response to food allergens by testing performed four and five years, respectively, after onset of symptoms. In one of these patients there was a positive allergic history on both sides of the family.

Follow-up Data in Thirteen of Eighteen Cases of Chronic Ulcerative Colitis in Childhood.—We were able to follow thirteen of the eighteen patients; eleven of them for eight to twenty-one years after the onset of the disease. The disease is now inactive clinically in four and chronically active in two. It was modified by surgical procedures in four; was fatal to three.

Inactive Cases: Only one of the four patients in whom on follow-up the disease has remained inactive was originally considered a severe case of ulcerative colitis.

Chronic-Active Cases: Two patients are still considered to have active chronic ulcerative colitis. They have severe symptoms of colitis and have suffered complications of the disease.

R. A. E., 22 years of age, after eleven years of intractable colitis, had crippling rheumatoid arthritis (acquired in the second year of her illness) and a mixed psychoneurosis. Roentgenologic signs of the existence of pseudopolyposis have been present from the onset of illness.

K. M., a 17-year-old female, has had chronic ulcerative colitis for thirteen and one-half years. Her illness has been complicated by arthralgia, pyelitis, and impetiginous cutaneous eruptions. This patient has since developed carcinoma of the colon and is discussed further in the section on carcinoma in chronic ulcerative colitis.

Surgical Cases: The four individuals treated by surgical means serve to emphasize what can and cannot be done with surgical techniques.

K. A., aged 11 years (1934), had the illness for four months. He was extremely malnourished and had a body physique channel beyond Wetzel's B_4 channel and was three years retarded in growth by comparison with Wetzel's 67 per cent standard auxodrome. Roentgenographically, the colon was narrow and ahaustral, with suggestive evidence of pseudopolyps. Two and one-half years later he showed an additional somatic retardation of one-half year and roentgenologic examination showed remarkable shortening and definite polypoid hyperplasia of the colon. As ileorectosigmoidostomy was performed nine and one-half years after onset of illness and one year later subtotal colectomy was performed. Following this he improved a little and gained height and weight. However, he maintained his B_4 channel, and at the age of 20½ years he had the physical development of a 13-year-old. One year later he developed intestinal obstruction and died.

The second patient treated surgically, B. E., a 12½-year-old white female (1946), had had chronic ulcerative colitis for six years. She had not gained any weight for three years. When first seen she was extremely thin. The caliber of her colon was remarkably reduced and it had lost the haustral markings. Her course was complicated by pyelitis. At the age of 16 years she looked like a 10-year-old preadolescent female without breasts or pubic hair. An ileosigmoidostomy was performed. Thereafter she ate more and gained weight, but still suffered with diarrhea. Colectomy was followed by further improvement. She remained ostensibly well for two years. She gained 34 pounds. A sudden exacerbation of her trouble then took place and typical lesions of ulcerative colitis were seen in the remaining segment of the rectosigmoid colon. With the use of Chloromycetin and ACTH she improved promptly. However, within the year another exacerbation occurred but this time she failed to

respond to cortisone, necessitating the performance of an ileostomy.

C. H. M., a white girl, aged 12 years, was admitted in 1948 with the complaint of having had a remitting bloody diarrhea for ten years. During the preceding two years she had had frequent episodes of edema of her arms and legs and once had a generalized crepitant swelling of the entire body. On admission here she was chronically ill, s t a r v e d, and underdeveloped. Wetzel Grid evaluation demonstrated a four-year deficit in physical growth. Her colon was short and ahaustral and possessed mucosal irregularities. Two years later, at the age of 14 years, having experienced frequent febrile exacerbations, she weighed only 45 pounds! An ileostomy was then performed. However, because of continuing fever and melena partial colectomy was required. The distal rectosigmoid was left. Following this operation her weight doubled within eighteen months. Though there has been no rectal discharge since, a rectosigmoidectomy has been advised. This child, who initially presented herself to us with a four-year deficit in physical growth and development, when last heard from five years later still showed a growth deficit of almost three years. Her reaction to the ileostomy is interesting. Her family physician writes: "She wears an ileostomy bag which fits perfectly. She rides horseback, dances, drives the car and seems like a normal individual—she went swimming with this boy every day for the past week—she is very popular with the boys and does not seem disturbed at all about wearing the bag." Such testimony is in contrast to Crohn's[1] statement regarding ileostomy in young unmarried women, namely: "An ileostomy is a complete frustration and denial of all romance, marriage and bearing of children."

The fourth patient, S. S. A., a white girl aged 13 years, had an extremely grave illness of four months' duration. Her illness ran a septic course, with a tremendous left shift in the Schilling differential, averaging 46 per cent stabs and younger forms in 27 white blood cell counts. Her illness was complicated by hypokalemia, hypocalcemic tetany, myocarditis, and many massive rectal hemorrhages. Two days before she was removed from the St. Louis Children's Hospital she appeared to be "moribund." She was taken from this hospital and admitted to another where surgical therapy was begun. She is now quite well.

Fatal Cases: A retrospective study of the fatalities serves as the basis for a tentative formulation of the indications for operative intervention.

There were three known deaths among the eighteen. One followed perforation of the colon, one attended an intestinal obstruction two years after the performance of an ileorectosigmoidostomy and colectomy, and carcinoma of the colon was the cause of death in the other. It appears that surgery may have been able to extend the life of the first and have obviated carcinoma in the third. The following is a brief case report of the first patient, the other two cases are discussed elsewhere.

T. A. E., a 12-year-old white male, was admitted in 1948 with a two-month history of fever and severe bloody diarrhea. Five months previously his father died, and following this the boy became very depressed and lost weight. This sequence of events might suggest psychogenic etiology but for the fact that ten and five months previous to his present illness he had had short-lived melena, which we now feel probably represents the onset of his ulcerative colitis. During a twenty-seven-day hospital course here his temperature reached 39° C. or higher daily. His stools numbered 4 to 16 daily, with from small to massive amounts of blood. In a total of nine white blood cell counts the stab forms ranged from 40 to 80 per cent. Despite supportive therapy, antibiotics, parenteral blood,

glucose, protein, and electrolytes, his course was progressively downhill. Following a massive rectal hemorrhage there was abdominal distention, and dilated loops of large and small bowel with fluid air levels were seen by x-rays. Death occurred on the third day of parenteral feeding. Autopsy revealed purulent adhesive peritonitis. The wall of the entire colon and terminal ileum was thick, boggy, and friable. Rows of polypoid mucosa extended the entire length of the bowel separated by deep ulcerated mucosa.

child was above average build, and it appears that this may have been an error in measurement since she was described as being "asthenic," and from the Wetzel Grid recording, one would expect her to be obese. Furthermore, such a body physique rating seems particularly suspect, considering that she was one of the most critically ill children observed. Five cases fell into the A_1MB_1 channel with good

TABLE I

CASE NO.	AGE (YR.)	DURATION OF DISEASE (YR.)	SEX	PHYSIQUE CHANNELS									AUXODROMES PER CENT					ACCELERATION OR RETARDATION IN YEARS OF GROWTH, COMPARED TO 67% STANDARD
				A_4	A_3	A_2	A_1	M	B_1	B_2	B_3	B_4	2	15	67	82	98	
1	3 10/12	2	F					V					V					2
2	12	10	F							V						V		−4
3	11 10/12	2/12	M									V				V		−4½
4	12½	6	F									V				V		−4
5	10 4/12	3	F						V						V			−1
6	8	5	M						V						V			0
7	12 4/12	9/12	F									V				V		−3
8	7	3½	F					V							V			0
9	9	4½	M								V				V			−1
12	14 9/12	5/12	M									V				V		−2¾
13	11	4/12	M									V					V	−3
14	4 2/12	1½	F						V				V					3
15	13	5/12	F	V										V				9/12
16	9	2	F						V					V				0
17	11 9/12	6	F									V					V	−2 9/12
18	10 4/12	8	M								V			V				9/12

EFFECTS OF ULCERATIVE COLITIS ON GROWTH AND DEVELOPMENT

Chronic ulcerative colitis during childhood is particularly capable of retarding growth and sexual development.

Adequate measurements for plotting body physique and development on the Wetzel Grid for evaluating physical fitness were available in sixteen of the eighteen patients at the time of their first admission to the St. Louis Children's Hospital (Table I). Only one physique; one was good to fair, two borderline, one borderline to poor, and six were poor or extremely thin, falling beyond the B_4 channel. Compared to the 67 per cent standard for age, nine of the sixteen patients showed retarded physical development, ranging from minus one to minus 4½ years. Seven of these nine patients showed more than two and one-half years' retardation of physical growth.

The retardation of physical growth associated with chronic ulcerative

colitis is also apparent in the fourteen cases reported by Benson and Bargen[2] in 1943. Plots of their data regarding height, weight, and age on the Wetzel Grid provide graphic evidence of phenomenal growth failure (Table II). The duration of colitis in their patients ranged from five to twelve years. The chronological age of their patients ranged from 15 to 22 years, but assuming a leveling off to speed of development (maturation) at age 16 in girls and 18 in boys and by comparing with Wetzel's standard age schedule of development, they showed a developmental age range of 7½ to 13½ years, with physical retardation ranging from 3 to 8½ years. The mean growth failure for the whole group was 5.7 years.

This general somatic retardation of growth is associated with delayed sexual maturation which may represent retardation of endocrinologic development. Our Patient 2, H. C., at age 14 "looked like a 9-year-old." She had neither breast development nor pubic hair. Another of our patients, B. E., at age 15 "looked like a girl of 10 to 12 years." She had not yet menstruated or showed any evidence of secondary sex characteristics. Thirteen of the fourteen patients of Benson and Bargen[2] showing failure of growth also showed pronounced delays in sexual development.

The retardation of growth and development associated with chronic ulcerative colitis appears to be more

TABLE II. GROWTH RETARDATION IN FOURTEEN CASES OF CHRONIC ULCERATIVE COLITIS (BENSON AND BARGEN)

CASE NO.	AGE (YR.)	SEX	DURATION OF COLITIS (YR.)	DEVELOPMENTAL AGE (YR.)	PHYSICAL RETARDATION (YR.)
1	22	M	12	10	8
2	16	M	7	9	7
3	16	M	6	9	7
4	16	F	5	7½	8½
5	15	M	8	8	7
6	18	F	6	13	3
7	17	F	9	9	7
8	17	M	7	13½	3½
9	17	M	7	13	4
10	17	M	7	12½	4½
11	17	F	5	11	6
12	15	F	12	12	3
13	16	M	6	11	5
14	17	M	7	9½	7½

TABLE III. FOLLOW-UP GRID EVALUATION IN CHRONIC ULCERATIVE COLITIS (ST. LOUIS CHILDREN'S HOSPITAL)

CASE NO.	DURATION COLITIS (YR.)	ACCELERATION OR RETARDATION COMPARED TO 67% STANDARD (YR.)	FOLLOW-UP IN YR.	FINAL EVALUATION COMPARED TO 67% STANDARD	FINAL PHYSICAL STATUS
1	2	2	6	5½	Well
2	10	–4	5	–2½	Well Ileostomy
7	9/12	–3	2	–2	Chr-act*
8	3½	0	8½	–1½	Chr-act*
9	4½	–1	1⅓	–1½	Active
13	4/12	–3	9½	–5	Chr-act*
14	1½	3	5½	1½	Chr-act*
18	8	9/12	2½	9/12	Chr-act*

*Chronic-active.

or less permanent. This is well shown in Table III. Patient 2, H. C., is especially pertinent. When first seen at 12 years of age she had a four-year growth deficit. Two years later an ileostomy was performed and this was followed by a subtotal colectomy. At the age of 17, after several years of relative well-being, she had doubled her weight and grown in height, but she still exhibited a two and one-half-year growth deficit and had the physical development of an average 13½-year-old child.

An examination of Benson's and Bargen's[2] reported cases (Table IV) substantiates our observations. In five of their patients with follow-up data we were able to demonstrate that despite subsequent clinical improvement on constant therapy with what appeared to be impressive gains in height and/or weight, these patients showed little or no improvement in Grid status and were nowhere near the standards for age.

Table IV. Persistent Growth Failure in Chronic Ulcerative Colitis (Benson and Bargen)

Case No.	Chronological Age (yr.)	Physical Age (yr.)	Deficit (yr.)
1	22	10	8
	24	12	6
5	15	8	7
	16	9½	6½
9	17	13	4
	18½	15	3
10	17	12½	4½
	23	15½	2½
12	15	12	3
	16	13½	2½

Each year of growth failure represents a tremendous caloric deficiency. Unless this "fuel debt" is paid, the patient cannot return to par, and growth failure with permanent stunting supervenes.

In chronic ulcerative colitis, growth failure is contributed to by decreased food intake from anorexia, by increased loss from diarrhea, by increased demands from fever and tissue breakdown, and last, but not least, the well-recognized ill effect on growth and development of associated emotional factors.

Under the most favorable circumstances, recovery from growth failure from any cause is slow and expensive—under the circumstances imposed by ulcerative colitis particularly if this be chronic or recurrent, recovery is well nigh impossible.

In the past, indications for surgical therapy in chronic ulcerative colitis have been outlined—a septic course, complications such as arthritis, perforation, carcinoma, etc. It appears that one should add severe and persistent growth failure. This applies particularly to the prepubescent child with severe chronic or recurring ulcerative colitis.

Carcinoma of the Colon in Chronic Ulcerative Colitis

Carcinoma of the colon is definitely more common in patients with ulcerative colitis than in unaffected comparable age groups. Kiefer and associates[3] found cancer of the large bowel to be 10-900 times more frequent among patients having ulcerative coli-

tis than cancer of the entire digestive tract is in the general white population.

Lynn,[4] in a collected series of cases, found an incidence of cancer of 1.9 per cent among 1,467 cases of chronic ulcerative colitis. In a collection of 2,540 cases (Table V) published since Lynn's[4] review, a similar incidence 1.6 per cent is found.

The actual incidence of carcinoma of the colon among persons of all ages having ulcerative colitis is not known exactly. Reported figures vary widely and are affected by several factors. One of these is the duration of the colitis. In 1948 Cattell[10] concluded from his experience that one out of three patients with ulcerative colitis who have had the disease more than nine years developed carcinoma. Another consideration in appraising true incidence is the series of origin from which the material is obtained. Surgical and autopsy material will have a higher incidence of malignant lesions. This is borne out by the findings of Kiefer and associates.[3] Their incidence of cancer in 214 surgical and 12 autopsy cases was 4.4 per cent, twice the incidence found in a group of 458 patients treated medically only. It would appear that this reflects cases referred for surgery because of clinically recognizable carcinoma, cases with prolonged duration predisposing to carcinoma and the unexpected finding of carcinoma in resected colons and in autopsy specimens.

Nevertheless, as Alvarez[11] and others have pointed out, it is not just the incidence of cancer that is so striking in these patients but the age of the patients so affected.

"In non-ulcerated colons one rarely sees carcinoma before the age of 40. One sees them usually after the age of 50 or 60."[17]

Ulcerative colitis appears to particularly predispose young persons to carcinoma of the colon if they have had ulcerative colitis more than five years.

TABLE V

AUTHORS	TOTAL NUMBER OF CASES ULCERATIVE COLITIS REPORTED	NUMBER OF CASES OF CARCINOMA	PER CENT (CA)
Renshaw and Brownell[5]	336	2	0.59
Ricketts and Palmer[6]	206	3	1.4
Kasich, Weingarten, and Brown[7]	143	7	4.9
Felsen and Wolarsky[8]	855	0	
Gleckler and Brown[9]	316	12	3.8
Kiefer, Eytinge, and Johnson[3]	684	19	2.7
Total	2,540	43	1.6

Jackman and associates,[12] comparing chronic ulcerative colitis in adults and children, found little difference in the percentage of all complications except carcinoma of the colon. The incidence of 6.3 per cent among ninety-five children having ulcerative colitis was twice the rate found in the 871 cases occurring among adults and children.

Table VI lists seven reported series with a total of 3,070 cases of chronic ulcerative colitis. In this collection there were seventy-two cases of carcinoma (2.3 per cent). In twenty-one of these seventy-two cases, or in 29.1 per cent, the patients affected with

carcinoma were less than 35 years of age! The youngest patient was 13 years of age, and had had chronic ulcerative colitis six years at the time the diagnosis of carcinoma was made. In ten cases in which the duration of colitis prior to the discovery of carcinoma was mentioned, the range was from 7 to 29 years, averaging 13.5 years. Of these ten patients six were male and four female.

Of 208,758 cases of cancer and other malignant tumors of the rectum, anus, and intestine (except duodenum) in all ages, both sexes and all races, during the years 1930, 1935, and from 1940 to 1945 (exclusive of deaths among Armed Forces overseas), 4,780 or 2.29 per cent occurred in patients below 35 years of age.[16] Calculations based on the Poisson distribution show that the probability of getting even as high as ten cases below age 35 in a sample of size 72 amounts to less than 0.00001. It is therefore safe to conclude that the probability of obtaining a value as high as 21 is vanishingly small.

This finding is very impressive and substantiates reported conclusions "it is therefore probable that carcinoma of the colon appears at an earlier age in patients with ulcerative colitis than in the general population,"[9] and even more foreboding in relation to the disease in children, "it is our impression that the incidence of neoplastic lesions is higher in those patients who develop chronic ulcerative colitis before the age of 20 years than in those of an older age at onset."[17] All but two of the ten patients in whom duration of colitis was mentioned had onset of ulcerative colitis before 20 years of age.

TABLE VI

AUTHORS	NUMBER OF CASES OF CHRONIC ULCERATIVE COLITIS	NUMBER OF CASES OF CARCINOMA	AGE OF PATIENTS UNDER 35 YR. WITH CARCINOMA	DURATION OF ULCERATIVE COLITIS (YR.)	SEX
Ladd and Fothergill[13]	26	1	13	7	M
Bargen and Coffey[14]	1,500	30	19		
			31	29	F
Helmholz[15]	65	1	20	10	M
Renshaw and Brownell[5]	336	2	31	9	M
			27	9	F
Kasich, Weingarten, and Brown[7]	143	7	22	16	M
			33	16	M
Gleckler and Brown[9]	316	12	25	9	M
			34	21	F
			35	9	F
Kiefer, Eytinge, and Johnson[3]	684	19	10 patients less than 35 yr. of age		
Total	3,070	72	21		

As significant as the percentage incidence and the age incidence of cancer in ulcerative colitis is the high degree of malignancy of these tumors and their multiplicity of origin. Of a total of 109 cases of carcinoma in patients with ulcerative colitis, Sloan and co-workers[17] found nine cases amenable to treatment by electrocoagulation, and excluding these, only three out of the 109 patients lived five years after surgical removal of the lesion. Bargen and Coffey,[14] referring to thirty cases of carcinoma, found multiple tumors in seven or eight patients

and several had "literally hundreds of them."

The problem is further complicated by difficulty in early diagnosis of cancer due to masking of symptoms by the underlying colitis so that most cases are inoperable when a resection is attempted.

Nor does inactivity of the disease process clinically give security in this regard. Helmholz's[15] patient died of carcinoma ten years after onset of ulcerative colitis and after four years of apparent recovery from this disease.

Two of our eighteen childhood cases of chronic ulcerative colitis, 11.1 per cent, developed carcinoma of the colon. J. W. died of inoperable metastatic carcinoma at the age of 23 years. He had had colitis for twenty-one and one-half years, the longest duration of illness we have followed up to the present. Subsequent to our initial follow-up, another patient is known to have developed carcinoma. K. M., a 19-year-old white female, after fifteen and one-half years of chronic ulcerative colitis complicated by arthralgia, pyelitis and impetiginous eruptions required ileostomy for recent recurrent intestinal obstruction. Subsequent colectomy revealed diffuse polyposis. Microscopic sections from multiple areas of the cecum, ascending colon, and hepatic flexure revealed foci of poorly differentiated adenocarcinoma infiltrating the bowel wall and mesentery.

Pertinent to this aspect of chronic ulcerative colitis is the incidence of polyposis which Helmholz[15] considered to be of "grave importance" and to "form ideal soil for the development of carcinoma." Five of our eighteen patients had polypoid masses, two on autopsy examination, one demonstrable at surgery, and two by x-ray examination.

Considering all facts, one is impressed not only with the real risk of carcinoma of the colon in protracted cases of chronic ulcerative colitis particularly if the onset be in childhood, but also with the wisdom of colectomy despite clinical improvement or well-being following ileostomy.

TABLE VII

EXTRACOLONIC COMPLICATIONS	NO. OF CASES
Pyelitis	5
Growth failure equivalent to more than 2½ years	7
Severe arthritis	2
Erythema nodosum	2
Hepatomegaly	4
Clubbing of fingers	2
Purpura	1
Recurrent edema	2
Metabolic disturbances	4
Hypocalcemia	
Hypokalemia	
Hypoproteinemia	
Pyodermia	1

EXTRACOLONIC COMPLICATIONS OF CHRONIC ULCERATIVE COLITIS

The extracolonic complications of chronic ulcerative colitis, though less dangerous than perforation, hemorrhage, or carcinomatous degeneration, are serious.

Among the eighteen patients, only three suffered no complications. Nine of the other fifteen had more than one complication (Table VII). The hypoproteinemia, the electrolyte changes, the hepatomegaly, and the growth fail-

ure are seemingly related to nutritional disturbances attributable to the diarrhea. There is no apparent etiological relationship between the colitis and such complications as arthritis, erythema nodosum, and recurrent edema of arms and legs with or without purpura. However, these latter complications must be related to the disease because they exist during the active phase of the disease and subside with the subsidence of the colitis. However, ultimately some of these complications may become irreversible.

Arthritis is a recognized complication of chronic ulcerative colitis. Sloan and collaborators[17] found arthritis in 7.7 per cent of 2,000 adults with colitis. Helmholz[15] discovered six cases of severe arthritis among sixty-five cases of chronic ulcerative colitis in childhood (incidence 9.2 per cent).

Five of our eighteen patients had symptoms referable to the musculoskeletal system. One had subjective joint pains and two others had joint swelling as part of a recurring edema of the arms and legs. These symptoms were associated with purpura in one case. Two others of the eighteen (11.1 per cent) had severe crippling osteoarthritis. R.A.E., when 12½ years of age, developed arthritis toward the end of the first year of illness. During the following two years she continued to have joint pains and swelling with each exacerbation of her colitis. The arthritic symptoms soon became so severe she could no longer attend school. Eight years later she was found to have a marked rotary scoliosis and lordosis of the lumbosacral spine, with great limitation of hip motion and enlargement of the left knee. Roentgenograms showed erosion of the intercondylar notch of the left femur, osteoporosis of the bones about the left knee, and signs compatible with recurrent hemarthrosis of the left knee.

The other patient having severe arthritis (G. J. A.) when 6½ years of age developed effusions in both ankles coincident with the very onset of his colitis. With the exacerbations of colitis he experienced attacks of migratory arthritis, involving at one time a knee, at another time a shoulder. When last seen at St. Louis Children's Hospital at the age of 14, and after seven and one-half years of recurring colitis, his right knee was larger than the left and contained 30 c.c. of cloudy yellow fluid when aspirated. Three years later he had severe poliomyelitis and developed a permanent flaccid paralysis of both legs. For the last four years his colitis has been symptomatically controlled.

The two cases of erythema nodosum seen in this series occurred in the above two patients. This suggests a common etiology for the arthritis and the erythema nodosum.

PSYCHOLOGICAL CONSIDERATIONS IN CHRONIC ULCERATIVE COLITIS

Currently, considerable attention is being paid to the psychological aspects of chronic ulcerative colitis.

Psychological references in the history and hospital records were made in seven of the eighteen cases. Two of the seven patients showed no psychological disorder by psychiatric examination. In another case, a fatal one, the child became depressed after the death of his father. However, the father died five months after the child's illness began with adiarrheal melena. One patient who suffered with severe recurrent colitis and crip-

pling arthritis had a psychological disturbance that was labeled as "schizoid type," eleven years after onset of her illness. In the other three patients emotional disturbances may have had some effect on the patient's comfort and the number of stools, but the psychological adjustments of these individuals were considered to be within the range of normal.

With reference to any particular type of personality predisposing to or characteristic of chronic ulcerative colitis it appears to us that it would not be easy to differentiate cause from effect.

For the mild, early, or remittent cases where psychotherapy would be maximally helpful, it is frequently not possible for economic or transportational reasons. After the disease is well established, though psychotherapy is of questionable value in arresting or altering the pathological physiology, it may be helpful in adjusting the child's emotional reaction to the physical illness.

For the acutely ill patient psychotherapy is not only impractical but may be hazardous. With fever, toxicity, severe diarrhea and bowel distention, psychotherapy is not any more likely to promote immediate improvement than it is in a case of an acute gangrenous appendicitis.

DISCUSSION

Though no attempt was made to elucidate the basic pathological physiology of chronic ulcerative colitis, some of our findings have possible bearing on pathogenesis.

In infancy and childhood as in adults asymptomatic melena is a common mode of onset. As early as 1923 Helmholz[18] was impressed with a case showing such an onset. Ten per cent of a series of 134 cases of ulcerative colitis in children collected by Lagererantz[19] had bleeding without diarrhea at the onset of their disease. In three of our cases blood by rectum, noted for months to years before diarrhea developed, was the first manifestation of the disease. These findings have been attributed to cases in which the disease process remains localized in the rectum or rectosigmoid. Rightfully so, recent studies in etiology devote considerable thought to the significance of such bleeding without diarrhea early in the course of chronic ulcerative colitis.

With regard to any primary relationship of allergy to this disease, the question always comes up of allergy acquired secondary to severe colitis on the basis of absorption of incompletely split foreign protein from the diseased colon. We see this course of events occasionally in small, artificially fed babies who, following severe diarrhea and parenteral feeding, appear temporarily intolerant of cow's milk protein after resumption of oral feedings.

Without meaning to deny or even to mitigate the psychiatric factors in etiology and maintenance of chronic ulcerative colitis, psychotherapy, for the reasons outlined, has limitations in the treatment of this disease.

This review serves best to emphasize the need of surgical therapy in chronic ulcerative colitis in childhood and to outline its indications. The criteria for surgical therapy in adults are well recognized—a prolonged course with failure to respond to medical therapy, severe and often irreversible extracolonic complications, acute toxic ulcerative colitis, and the various surgical emergencies such as perfora-

tion, exsanguinating hemorrhage, and carcinoma. Though these same exigencies exist in children and admittedly to a greater and more severe degree still one somehow hesitates to perform colectomy with ileostomy in the young patient. Too often because of such procrastination the colon is saved but the patient is lost.

Our eighteen patients ran the gamut of almost every known complication. Some of these, such as arthritis, can be permanently disabling as demonstrated by two of our patients (R. A. E., G. J. A.). To prevent irreversible changes, Crile[20] lists recurrent arthropathy as one of the major criteria for early colectomy. Reviewing our cases from this standpoint alone such therapy seems indicated.

One patient (T. A. E.) died of acute toxic ulcerative colitis with perforation. Another (S. S. A.) with an equally fulminant course was saved by surgery elsewhere. In retrospect we can but agree with Ferguson and Stevens[21] that such patients are "too sick not to be operated upon." The chief cause of death in these cases of acute febrile toxic ulcerative colitis, of either recent origin, or with acute exacerbations of long-standing ulcerative colitis, is perforation and peritonitis. It is hard to understand the hesitency in performing surgery in these cases of acute toxic febrile ulcerative colitis considering our zeal in early surgery with other lesions threatening perforation and recognizing the cardinal surgical principal of débridement and removal of necrotic tissue. As Crile and Thomas[22] put it, these colons are like third-degree burns bathed in a fecal poultice. No matter what the operative mortality is in cases such as these, it is higher still without surgery and undoubtedly would be less formidable if surgery was not done as a last resort. Because of the frequency of reports of temporary improvement with ileostomy being followed by fatal perforation or hemorrhage, colectomy is a necessary evil. Furthermore, if the colon is not removed, the patients "do not often obtain remission sufficiently complete to allow them to resume their social and economic activity."[22] When faced with this decision, the theoretical advantage of the removal of necrotic, ulcerated, potentially malignant colons is supported by the practical experience of Crile[20] who found that ileostomy and colectomy carry a lower mortality than ileostomy alone. His latest mortality for colectomy in cases of acute toxic ulcerative colitis is 13.3 per cent (two deaths out of fifteen cases). This is one-fourth the mortality rate in patients treated with ileostomy alone or conservative treatment. He reports a zero mortality in thirty-five patients with chronic ulcerative colitis subjected to subtotal colectomy and ileostomy and for removal of the rectal stump.

Evidence is also presented that malignant degeneration is a real risk in chronic ulcerative colitis of prolonged duration, particularly with an onset of the disease in childhood. These facts further support the wisdom of colectomy despite apparent improvement or continued well-being following simple ileostomy. Though only two of our eighteen patients have developed inoperable metastatic carcinoma (to date), at least one other (R. A. S.) is a good candidate by virtue of onset in childhood and being well into the second decade of chronically active ulcerative colitis. Furthermore, in this particular patient polyposis was

evident from the very onset of her illness.

In addition to these accepted criteria for surgical treatment we would like to recommend for consideration severe growth failure. Unquestionably chronic ulcerative colitis during childhood and adolescence is often accompanied by significant permanent retardation of the rate of growth. It might be said that chronic ulcerative colitis may be considered as one of the causes of dwarfism and suggests that the developmental and endocrine disturbances attending ulcerative colitis may not be entirely relatable to chronic starvation.

CONCLUSIONS

Chronic ulcerative colitis in children is relatively more serious than in adults. Certain complications are of particular interest in this age group. With chronic or recurrent colitis, severe growth failure is inevitable. Carcinoma, a recognized complication in cases of prolonged duration (usually more than seven years), appears to be more common in patients who develop the disease in childhood.

For the present and until such time as definite etiology is established, in certain cases surgery is mandatory; this applies particularly to acute toxic ulcerative colitis and to cases with threatening sequelae — arthritis, severe growth failure, and malignant degeneration. Furthermore, such surgery should entail colectomy and not ileostomy alone and probably the colectomy should be complete. Admittedly such therapy is drastic, but even considering all the drawbacks it is the lesser of the two evils.

In conclusion it appears to us that medical therapy should be reserved for mild to moderate cases of colitis, provided there are no serious complications and the course is not too prolonged.

We wish to thank Dr. Carl A. Moyer for his critical advice in the preparation of this paper.

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EFFECT OF DIFFERENT TYPES OF IMMUNIZATIONS PROGRAM ON DURATION OF DIPHTHERIA IMMUNIZATION AS INDICATED BY SCHICK REACTIONS

MARJORIE K. SMITH, M.D.
NEW YORK, N. Y.

RECENTLY the use of the Schick test to indicate immunity to diphtheria has greatly decreased. Immunization of children has become almost routine. When doubt arises as to a child's status, he is more likely to be given a booster injection than a Schick test. Rosenau[1] in 1927 stated that by the age of 20 years 88 per cent of the population would have developed a natural immunity.

In 1933 it was believed that in urban areas 80 per cent would be Schick negative by the tenth year; in rural communities the proportion was considered less.[2] By 1940 Thomson and Glazebrook[3] found 70 per cent of university students from well-to-do families and 35 per cent of military men from poor families gave positive Schick reactions. Today, about 50 to 60 per cent of adolescents and adults are nonimmune.[4]

In Massachusetts in 1920 the diphtheria incidence was 8,000; in 1946 to 1949, 300 to 400; in 1953, 31. There was marked increase in morbidity, however, in adults and adolescents and an ominous rise in case fatality in these groups. By serology tests, Ipsen and Bowen[5] of the Biological Laboratory of the Massachusetts Department of Public Health found 55 per cent of individuals over 20 years of age were nonimmune. These figures support the impression that most diphtheria today is in adults.

In three areas widely separated geographically and of differing socioeconomic status, Schick surveys were made to check on the efficiency of local immunization programs. The data show close correlations.

The three surveys were made in (1) Longview, Washington, public schools, December, 1943, and March, 1949; (2) Flint, Michigan, public schools, January, 1951; and (3) Judson Health Center, lower west side New York City, January, 1955.

Longview was a rapidly growing industrial city of 15,000 to 20,000 with the population mainly Nordic in ethnic background with many new arrivals from the South and Midwest. Children in all grade schools (kindergarten to eighth grade) were tested here.

Flint was an industrial city of 110,000 with many transients and a large influx of Negro people from the South. One school tested had a 50 per cent change of population in the school year. Pupils in one grade school (kindergarten to sixth grade) predominately white, one grade school, 98 per cent Negro, and a junior high school 25 per cent Negro were tested.

Judson Health Center is a family service health center in the crowded

Address: 34 Spring St.

lower west side of New York City with relatively stable population. About 75 per cent of the clients are Italo-Americans, 10 per cent Puerto Rican, and the remainder of widely divergent racial backgrounds.

In Longview, before 1943, there had been no great stress on immunization. Many children had had only one injection; immunization in infancy had been considered adequate for life; and many came from places where immuni-

TABLE I. IMMUNIZATION STATUS

	NO.	AGES (YR.)	GRADES	POSITIVE SCHICK TESTS NO. PATIENTS	POSITIVE SCHICK TESTS PER CENT	PREVIOUSLY IMMUNIZED	NOT PREVIOUSLY IMMUNIZED
Longview, Wash.							
Dec., 1943	1,201	5-13	kg-6	449	37	652	549 (45%)
Tested	260	12-15	7-8	±96	±37		
March, 1949, enrollment	3,397	5-15	kg-8			3,199 (94%)	198 (5.8%) status unknown or never immunized
Immunized, 1948	1,558	5-15	kg-8	Not tested			
Schick tested	1,718	5-15	kg-8	445	25		
Flint, Mich.							
Enrollment, 3 schools	1,516	5-16	kg-9				
Tested March, 1951	1,225	5-16	kg-9	609	50		
Judson Health Center, New York City							
Tested	100	3½-18	Clinic	40	40		

In the original series (1943, Longview) only the kindergarten and first six grades were tested. No attempt was made to check by date of previous immunization. In general, few had been immunized later than the first grade. There were so many Schick test positives in the fifth and sixth grades that it was decided to test the seventh and eighth grades. Unfortunately, the schools were closed because of an influenza epidemic after Schick tests were given and before the reading was possible. There were ninety-six unsolicited written requests from parents for immunization on the score that their child had a red reaction. In all probability this did not include all positives. It can be conjectured that the percentage probably paralleled the findings at Flint.

TABLE II. DISTRIBUTION OF POSITIVES BY TIME INTERVAL AFTER IMMUNIZATION

POLICY	FREQUENT BOOSTERS	IMMUNIZATION BEFORE ADMISSION TO SCHOOL	IMMUNIZATION BEFORE ADMISSION TO SCHOOL
TIME INTERVAL	LONGVIEW, 1949 (1,718)	FLINT, 1951 (1,225)	JUDSON HEALTH CENTER, 1955 (100)
1¼-2¼ yr.	1947 27% 125 of 463	1949-50 25% 34 of 137	1952-53 27% 8 of 29
2¼-3¼ yr.	1946 25% 126 of 502	1947-48 43% 89 of 208	1951 48% 11 of 23
3¼-4¼ yr.	1945 28% 98 of 351	1946 52% (original fig.)	1950 54% 7 of 13
4¼ or over	1944 34% 96 of 402	1945 56% (not available)	1949 40% 14 of 35

RESULTS BY SCHOOLS IN FLINT

	ENROLLMENT	NO. TESTED	NO. POSITIVE	PER CENT POSITIVE
1. Grade school 98% White (kg-gr.6)	391	312	121	39
2. Grade school 98% Negro (kg-gr. 6)	392	339	168	50
3. Junior high school 25% Negro (gr. 7, 8, 9)	733	574	320	56

Records of past immunization were relatively complete in all areas. Immunization programs in the three cities were somewhat similar.

zation was considered unnecessary. After this survey most pupils having positive Schick reactions were immunized. Then a program was instituted

so that after a two-year period a booster injection was given. Beginning in 1947, when it was believed that most children were probably immune, the interval between immunizations was lengthened to three years. Alum-precipitated diphtheria toxoid was used, except that in 1947 and in 1948 the combined tetanus, diphtheria, and pertussis antigen was given to children in the kindergarten and first two grades. Reactions following immunizations were practically nil. School absenteeism did not increase. Children from kindergarten through the eighth grade participated in this program.

In Flint, the stress had been to have all children immunized once previous to or about the time of admission to the schools. Usually there had been a complete immunization or a booster injection before entering kindergarten or first grade. Older nonimmunized children coming from other areas were encouraged but not required to be immunized. No program for booster injection was in force.

At the Judson Health Center children were immunized on a schedule closely approximating that of the current New York City health program as applied in the health stations and schools, immunization followed by a booster injection at about two years and another before entering school. Children in the older age group had been immunized only in infancy or on admission to school. The children at the Judson Health Center ranged from 3½ to 18 years, and the interval since last injection was from eighteen months to fifteen years.

Although in Flint there had been a much stronger health program in the school of predominantly Negro population, the percentage of positive Schick reactors was much higher than in comparable groups in the school 98 per cent white. Of those in kindergarten and first grade 46 and 54 per cent were positive in comparison with 21 and 40 per cent in the other school.

The limited number tested at the Judson Health Center closely followed the pattern at Flint and the first Longview survey. That is a marked increase in the number of positive reactors after two years. In the 1943 Longview survey 41 per cent of the positive reactors had been previously immunized at some time. The percentage in the fifth and sixth grades was unexpectedly high.

After the immunization program had been instituted in Longview it was observed that 72 to 75 per cent were protected for four years and 66 per cent for five. This contrasted sharply with about 45 per cent loss of immunity by the third year where repeated immunizations were not in force.

SUMMARY

Schick-testing programs involving 3,500 children in Longview, Washington, Flint, Michigan, and New York City were analyzed in relation to local immunization programs.

Where immunizations had consisted of only preschool inoculations about 75 per cent were protected for two years and 50 per cent for three. Approximately 55 per cent of the children never immunized were Schick positive; 56 per cent of 733 junior high school pupils were Schick positive irrespective of immunization history.

Among 1,718 Longview children tested after a six-year program of two- to three-year interval booster injections, the precipitous fall from 25 to 50 per cent at the third year did not

occur and 66 per cent remained protected over four years.

There were no severe reactions among the older children immunized with the alum-precipitated diphtheria toxoid.

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On the Hooping-Cough or Chin-Cough

The hooping-cough, like the small pox, measles, and the venereal disease, never appeared in Europe originally, but was transported thither from other parts of the world by means of merchandise, sea-men, and animals: it was a new disease to our ancestors in Europe, and probably was conveyed to them either from Africa or the East-Indies, where it was rooted before. Its first appearance in Sweden cannot be determined with any certainty; but in France it began in the year 1414.

It is likewise observable that the hooping-cough always appears as an epidemical disease. I think its nature is easily to be understood, since I have many times plainly perceived it to be contagious, and that it infects only such children who have not yet had it.

A person who has once had the hooping-cough is as secure from the danger of catching that disorder again as those who have had the small-pox and measles are with regard to those respective diseases. During my practice I never found or heard of any one who had been infected with the hooping-cough more than once.

It comes on only by degrees, and is at first dry, but when it has continued ten or twelve days, it turns humid, and the matter which is then coughed up looks ripe; nevertheless it increases more and more, leaving long intervals; the fits return at certain hours, but continue at each time with such violence and for so long a time, that the child grows blue in the face, its eyes look as if they were forced out, and they run besides, and a bleeding of the nose is sometimes brought on; it coughs till it is quite out of breath, that one is in apprehension of its being choked; for if the patient now and then is capable of drawing some breath, it is with a sounding which very much indicates with what difficulty the lungs can admit the air. The coughing continues, and does not leave off for that time, till the child vomits up a quantity of slime.

. . . for the disease is both tedious and severe. When it is left to the course of nature alone to be worked out, it commonly will last eleven to twelve weeks, nay frequently half

(Continued on page 299.)

KEROSENE POISONING IN CHILDREN

A Study of 204 Cases

Wm. D. McNally, M.D.
Spring Hill, Ala.

THE accidental ingestion of kerosene by children is the most common cause of poisoning in the South. Bain[1] reports that petroleum products were responsible for 25 per cent of the deaths of children under 5 years of age in the United States during 1949 and 1950. The regional death rates for twelve southern states for accidental poisoning in children under 5 years was 1.41 per hundred thousand for petroleum products. This is nearly four times the rate for aspirin and salicylic acid poisoning.

The purpose of this paper is to review the major findings of the 204 cases of kerosene ingestion admitted to the City Hospital, Mobile, Alabama, from 1946 through 1954 (Table I), to review the therapy and strike a keynote for labeling of kerosene and similar poisons *as* poisons.

Table I

Year	Kerosene Ingestions Admitted	Deaths
1946-50	60	6
1951	64	
1952	16	0
1953	24	0
1954	40	0

Abject parental carelessness was responsible for all of these poisonings. Kerosene was left in glasses, cups, and beverage bottles easily accessible to the children who had previous occasion to drink from these same containers.

The age of the children ranged from 8 to 60 months, with an average of 20.5 months. The youngest of this group was given kerosene instead of water in a nursing bottle with fatal results. In the majority of the cases the amount of oil ingested was not definitely known, varying from a few to 180 c.c.

The average hospitalization was three days, ranging from less than twenty-four hours to sixteen days. The patients having the longer stay in the hospital were those admitted after three hours of ingestion of the kerosene or those who did not have a mineral oil lavage upon admittance. Most of the patients were admitted within forty-five minutes of taking the kerosene.

All of the children showed upper respiratory tract symptoms. Five developed dyspnea and eleven became cyanotic. Physical signs in the chest were slight in the majority of the cases, but râles and rhonchi were heard in twenty of the patients. Of the total number of cases only 30 per cent were diagnosed as pneumonia. Since many of these children did not have x-ray examinations prior to 1950, it is possible that some of them may have had pathology in the lungs not diagnosed clinically. Three developed pneumonia

where there was no history of vomiting or lavage after admission.

Less than 10 per cent of the patients prior to 1954 had chest roentgenograms, 47 per cent of the patients in 1954 had positive roentgenographic evidence of pneumonia following the ingestion of kerosene.

The roentgenological reports of the chest varied from patchy infiltrations to a diffuse interstitial pneumonia of both lungs. Most of the x-ray examinations were made twenty-four hours after admission. Foley and colleagues[2] report finding in a radiograph taken twenty-five minutes after a child had swallowed or aspirated kerosene, "small scattered areas of cloudlike density in each lung base with more extensive confluent clouding noted in both lower lobes, especially in the basal segments twenty-four hours later." In 80 per cent of patients with positive findings there was involvement of portions of all lobes of both lungs. Complications such as empyema, pneumothorax, and pleuritis have been reported by Lesser.[3]

Gastrointestinal symptoms occurred in 27.5 per cent which is much less than the 69 per cent reported by Foley.[2] However, this can possibly be explained upon the premises that 80.5 per cent of our cases were Negro, and adequate histories were not obtainable. Two patients had blood-streaked vomitus. Two others had occult blood in stool specimens, which were negative for pathogenic bacteria and ova, cysts, and parasites.

Forty per cent of the patients were lethargic, eight were semicomatose and none had convulsions. Central nervous system symptoms were more prominent in the children taking the larger amounts of kerosene or those that were not brought into the emergency room early. However, listlessness and somnolence were prominent symptoms, even in those patients with a history of ingesting small amounts of kerosene. This was true, too, in those patients brought for emergency treatment within twenty minutes of taking the kerosene, indicating marked susceptibility and rapid absorption in children under 5 years of age.

Richardson and Pratt[4] report from animal experiments "the results in general appear to underline the outstanding importance of aspiration, and to minimize the role of gastrointestinal absorption." On the basis of their findings it is difficult to conceive of a child drinking a sufficient quantity of kerosene to produce a fatality by absorption from the gastrointestinal tract alone. Translated into terms of a child of 50 pounds a volume in excess of one pint would be the minimal lethal dose without aspiration.

Diechman and associates[5] submit evidence that injury to the lungs results from absorbed kerosene carried by the blood stream as well as by aspiration with the former of greater importance. Working with rabbits Diechman found the lethal dose for this animal to be 28 ml. per kilogram.

Most patients had normal temperatures upon admittance, but in 87 per cent rectal temperature rose rapidly, ranging from 100 to 105.8° F. with associated tachycardia.

Urinalysis showed the presence of albumin in 30 per cent of the cases, varying from a trace to three plus. Reducing substances were found in six specimens and three had acetone. Sev-

eral showed a few red and white cells per high-power field.

Blood counts were done upon 85 per cent of the patients. The white count varied from 4,500 to 31,900, with 73 per cent of the patients having counts over 10,000. The white count on patients not having pneumonia ranged from 7,850 to 19,500, with an average of 11,890. The lymphocytes ranged from 10 to 79 per cent, with an average of 33 per cent. The hemoglobin varied from 7 to 11.5 grams.

Some of the children were returned to the hospital for other conditions and did not have any ill effects from the ingestion of the kerosene; however, there was no routine follow-up of these cases.

The ages of the children dying from the effects of the kerosene were 8 to 25 months. All died under twenty-three hours after admittance to the hospital, one dying within two hours. There have been no deaths in the last three years.

Prior to 1951 the treatment was not standardized. Some patients were given ipecac, a few were given caffeine sodium benzoate, a few had a lavage, and nearly all were given antibiotics. The routine treatment at the City Hospital for patients that are admitted is immediate gastric lavage with 2 ounces of mineral oil. Another ounce is then left in the stomach. If the child has vomited or is not drowsy the lavage is omitted. Every child is given 300,000 units of penicillin when admitted to the ward and 0.5 c.c. of caffeine sodium benzoate in all cases of drowsiness or depression. Penicillin is given every four hours until the temperature is normal. Where respiration is labored the child is given ½ c.c. of Coramine and put under an oxygen tent. When gastric lavage was not instituted, or the child admitted several hours after swallowing the kerosene, the hospital stay was more protracted and involved. Reed and coworkers,[6] using rabbits, found no pulmonary damage after the animals had received kerosene orally. They concluded that pulmonary changes were the results either of primary aspiration or of aspiration secondary to regurgitation or vomiting. In this series of cases a number of children who had not vomited or been aspirated were drowsy, developed temperatures, and were very ill for twenty-four hours after admittance, recovering in forty-eight hours.

SUMMARY

1. A statistical study of the outstanding features of 204 cases of kerosene poisoning is given with pulmonary involvement as the most serious complication, with the conclusion that lavage with mineral oil should be given to all patients.

2. The dangers of accidental poisoning by kerosene and the measures necessary to prevent its ingestion by small children should be stressed repeatedly by health education to the medical profession and the public. Parents should be just as cautious about kerosene as they are about other toxic substances about the household. As the oil is purchased in gallon jugs in most instances, it bears no label of caution to inform the public that it is a poison. The children under 5 years of age are especially receptive to eat or swallow poisonous substances because of their mental and physical immaturity and the accompanying lack of judgment. In the case of petroleum

products, laws could be enacted to label as poison, with precautions, the containers sold to the public. Next, educate the public through the press, radio, and television of the dangers of leaving all toxic household articles and drugs within the grasp of these young children.

3. More cases of poisoning occur in children from kerosene than from lead each year, and all containers of kerosene should have labels with the SKULL and CROSS BONES, with the word POISON in red letters, setting forth the dangers and measures to prevent accidental poisoning. A law should be introduced preventing buyers of bottled beverages using returnable bottles when empty to store poisonous substances.

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a year. What is still worse, the disease is very dangerous and often fatal. A number of patients are stifled by it, getting convulsions and apoplexies, others pine away entirely, others again are puffed up by it and die.

The cure might easily be obtained if we knew any remedy which had a specific power of killing this seed or making it inactive. . . . Last year, 1770, seal's fat began to be used against the chin-cough; half an ounce was boiled in a pint of milk for a quarter of an hour. Of this milk was given a table spoonful morning and night to children at the age of a year or half a year, giving more in proportion to those who were older. It is assured that the worst symptoms (as the child being out of breath and nearly stifled) went off within eight days, but the coughing continued for a longer time. This however was likewise afterwards cured with a few drops of tar mixed with the yolk of an egg. Doctor Morris . . . mentions likewise that he has heard of children being cured within nine or ten days by the peculiar rank stench which comes from a goat or a fox.

ROSEN VON ROSENSTEIN'S "DISEASES OF CHILDREN AND THEIR REMEDIES" (1771)

RESULTS OF CORTISONE AND ACTH TREATMENT OF RHEUMATIC FEVER

MANES S. HECHT, M.D., WARREN E. SHELDEN, M.D., ANTHONY NOLKE, M.D., DOROTHY HOFSTRA, M.D., AND EDITH WEST, M.S.
DETROIT, MICH.

THE administration of cortisone and ACTH in treatment of rheumatic fever was first reported by Hench[1] in 1949. Since then, numerous articles on the subject have appeared, attesting the widespread use of this form of therapy, but not establishing its value beyond question. The reports of Barnes,[2] Dorfman,[3] and their associates, Bunim,[4] Massell and Warren,[5] and many others, while guarded, suggest some advantages of hormone treatment. V. C. Kelly,[6] Greenman and coworkers,[7] and more recently Heffer and associates,[8] felt that they have prevented cardiac damage in early cases. Wilson and Helper[9] were most enthusiastic. Kuttner and coworkers[10] have expressed the belief that ACTH and cortisone may be lifesaving in severe cases. This view is widely held. Taran and collaborators[11] pointed out the danger of severe recurrences after withdrawal of hormones. Rowe and associates[12] considered salicylates still the most practical form of treatment. Johnson and Ferenez[13] compared the cases of 100 cortisone- or ACTH-treated patients with eighty cases of the precortisone era and found no significant difference in the incidence of residual heart disease. The American Heart Association[14] set up an elaborate controlled study in which thirteen clinics participated. This group issued a preliminary report, finding no significant difference up to that time between the results of cortisone and ACTH or salicylate therapy. This work has been criticized[7] on the grounds that the dosage schedules of hormones were too low. It is not our purpose to review the literature but to point out that differences of opinion exist. Massell[15] has published a comprehensive review of the subject.

We shall present the results of cortisone and ACTH treatment of patients with rheumatic fever admitted to the Children's Hospital of Michigan between April, 1950, when we first employed this treatment, and September, 1953, stopping at that point to allow at least a full year follow-up for every patient. The cases presented in our earlier report[16] are included in this study. We have also reviewed the records of our rheumatic fever patients admitted to the hospital from December, 1946, to April, 1950, and shall compare the results obtained during that period

From the Department of Pediatrics, Children's Hospital of Michigan.

Delivered at the Regional Meeting of the American Academy of Pediatrics at Detroit, Michigan, April 4, 1955. This study was aided by a grant from the Michigan Heart Association.

Much of the cortisone used was donated by the Merck & Company, Inc.

with the hormone-treated patients in two respects, the disappearance of apparent valve lesions and the number of deaths. All our patients are children who were 12 years of age or less when treatment was begun.

CRITERIA FOR ADMINISTRATION OF HORMONE

When we first used the hormones we were hampered by an inadequate supply, and we were rather afraid of these potent substances. Our first patients were extremely ill children who had become worse while on salicylate therapy. After a time we were convinced of the superiority of cortisone and ACTH in severe cases and began to give these substances to less seriously ill children in the hope of lessening residual cardiac damage. After a few months we reached our present criteria of selection. Barring contraindication, such as recently active tuberculosis, we administered cortisone or ACTH to most patients with active rheumatic fever who had demonstrable carditis. If the evidence of carditis was limited to prolongation of the P-R interval, we usually started treatment with the salicylates, but changed to cortisone if the response was unsatisfactory. Patients who did not exhibit evidence of carditis were treated with salicylates, usually in the form of aspirin, ¾ grain per pound per day. These patients were watched closely and cortisone therapy was instituted if signs of carditis appeared. This was seldom necessary.

Table I shows the composition of the entire group of rheumatic fever cases for the period of hormone therapy. There were 255 patients, of whom fifty-five were private patients, the remainder staff cases. Nineteen private patients treated with cortisone or ACTH by various staff members have not been included in our results because of the difficulty in obtaining uniform follow-up. There were 122 hormone-treated patients who were under our control during treatment and convalescence. Most of these were followed in our rheumatic fever clinic, a few were under the care of private physicians. Several have moved away or have failed to return recently but all have been followed at least one year and the great majority remain under observation. One hundred fourteen patients did not receive cortisone or ACTH. Five of these died; their cases will be discussed later. A few were inactive and therefore untreated. Most of this group had relatively mild attacks which were treated with salicylates.

TABLE I. RHEUMATIC FEVER ADMISSIONS APRIL, 1950, TO SEPTEMBER, 1953

	NO.	VALVULAR LESIONS	CARDIAC FAILURE	CARDIAC ENLARGEMENT
Staff-controlled cortisone or ACTH	122	90 (73%)	27 (22%)	40 (32%)
Private cortisone or ACTH	19	9	2	3
Salicylates or no treatment	114	32	6	11
Total	255	131 (51%)	35 (13%)	54 (21%)

CHOICE OF HORMONE

Our first group of forty-four patients were about equally divided between ACTH and cortisone therapy. In the more recent cases we employed

oral cortisone because of the greater ease of administration. In a few instances severely ill patients were given ACTH for a few days, then oral cortisone. Recently we have given short courses of ACTH to patients at the termination of long periods on cortisone.

DOSAGE

We have not employed set dosage schedules but made a point of trying to meet individual needs. Our aim has been to suppress fully rheumatic activity yet avoid unnecessary excess. Cortisone is administered orally every six hours. Daily dosage in most cases in this group has been as follows:

300 mg. for 1 day
200 mg. for 3 to 7 days
150 mg. until evidence of activity is suppressed, usually 2 weeks
100 mg. for 3 to 4 weeks
75 mg. for 4 days
50 mg. for 3 days

Recently we have maintained the 150 mg. level longer, and the 100 mg. level for shorter periods. In most cases 150 mg. per day will keep rheumatic activity apparently suppressed. Small children may need only 100 mg. but very few can be maintained on less. Some patients, especially the larger children, require 200 mg. or even 300 mg. daily to maintain suppression of rheumatic activity. We have "tapered off" rather abruptly on the theory that small doses do not suppress rheumatic activity but may delay the reactivation of the patient's adrenals. When cortisone has been maintained for eight weeks or longer, we taper medication off in two weeks instead of one. Recently we have administered ACTH, 40 to 60 mg. daily for four to seven days after termination of longer courses of cortisone. A few, who were nauseated when admitted to the hospital or who had rapidly progressive disease, started on ACTH, usually 25 mg. every six hours, and changed to oral cortisone a few days later.

DURATION OF TREATMENT

Table II refers to time on therapeutic dosage, usually 100 mg. per day or more; tapering-off period is not included. Patients who received more than eight weeks of such treatment were, in the main, children who received additional treatment because of posthormone relapse.

TABLE II. DURATION OF TREATMENT

WEEKS	NO. PATIENTS
Less than 4	8
4 to 6	55
6 to 8	36
8 to 10	15
10 to 12	5
More than 12	3
Total	122

PRECAUTIONS

These patients were hospitalized throughout hormone treatment and for as long after as we thought necessary to observe them for possible relapse. Bed rest was maintained throughout treatment and thereafter until we felt reasonably sure that rheumatic activity had subsided. Most of these children were transferred to our convalescent home for an additional period and in all cases return to physical activity was carefully regulated. All patients on hormone therapy were fed low sodium diets and received medicinal potassium. All our patients with rheumatic fever received intramuscular penicillin for the first three days and then oral penicillin for the duration of the hospital

period. In the convalescent home either sulfadiazine or penicillin prophylaxis was employed and maintained after discharge.

All essential laboratory procedures have been utilized and all necessary supportive measures have been carried out. Patients with cardiac decompensation have been digitalized and oxygen and diuretics have been used as indicated. Occasionally small transfusions of packed red blood cells have been given to anemic patients.

SIDE EFFECTS

We have not found it possible to give enough cortisone or ACTH to suppress rheumatic activity without producing some signs of the Cushing syndrome. We have disregarded moon face, obesity, and hirsuitism. These have disappeared later except for some children who had large appetites and remained overweight. We have observed transient mild glycosuria and moderate elevation of blood pressure. White blood cell counts have frequently risen during treatment to about 20,000 predominantly polymorphonuclear leukocytes, without evidence of infection. Abdominal distention often occurred early in the course of hormone administration. This added to the respiratory embarrassment of decompensated patients. The salt and water retention effect of cortisone and ACTH added to the difficulty of managing children in cardiac failure. We were alert to the possible occurrence of masked infection but did not find any. Various overt intercurrent infections did occur. There were a few cases of chicken pox, measles, and mumps. The first such patients were taken off hormone treatment with resultant rheumatic relapse in some. Later, cortisone was maintained throughout the intercurrent disease without apparently altering its course. There were a few pyogenic and respiratory infections which responded to appropriate treatment. One child had concurrently severe rheumatic fever and brain abscess. She recovered from her attack of rheumatic fever but died later of the brain abscess.

RESULTS

For results, see Table III.

TABLE III. HORMONE-TREATED PATIENTS

NO.	COMPOSITION		
	DECOMPENSATED	VALVULAR LESIONS	CARDIAC ENLARGEMENT
122	27 (22%)	90 (73%)	40 (32%)
	Results		
Signs of valvular lesions disappeared		24	(19%)
Heart size decreased		25	(20%)
Heart size increased		7	(5%)
Deaths from rheumatic fever		3	(2.7%)
Deaths from other causes		1	
Recurrences		16	(13%)
Long-continued low-grade activity		7	(2.7%)

Valvular Lesions.—For brevity, all valvular lesions have been grouped together. As would be expected in this age group, mitral insufficiency was by far the most common lesion. By disappearance of signs of valvular lesions we mean the loss of signs during the course of treatment.

Heart Size.—For the purpose of this paper we have classed as enlarged hearts those for which cardiothoracic ratio was .53 or greater. By increase or decrease in heart size we mean a variation of .03 or more in the cardiothoracic ratio.

Moderate increases in the size of the heart shadow sometimes appear early in the course of hormone therapy in patients who otherwise seem to be responding well.

Deaths.—All deaths occurred in patients who were in cardiac failure at the time of admission. One child lived six months but was never fully compensated during that time. The second child died suddenly about one month after treatment was started. She was only mildly decompensated at the time of her death. Autopsy was not permitted. This patient had had active tuberculosis a year before and was treated with ACTH only because she did not respond to salicylates and was so ill it was thought that she would die of hormone treatment was withheld. A third child who died was first treated for a recurrent attack which he survived with a huge, badly damaged heart. He was treated again for a recurrence about a year later but not successfully. The child who died of brain abscess showed at autopsy a mitral insufficiency but no evidence of rheumatic activity. Among patients admitted between September, 1953, and January, 1955, not included in this report, there have been two additional deaths.

Relapse.—The most difficult decision in the course of hormone treatment of rheumatic fever is that of when to stop. The medication suppresses the usual laboratory and clinical evidences of activity. We have found no tests, including mucoprotein determinations, which give reliable indications of the probability of relapse after medication is stopped. It has been our impression that patients with rapidly progressive carditis before treatment, those with histories of prolonged activity before treatment, and those who require high dosage of hormone for suppression of activity, are the ones mostly to relapse. Such patients have been given longer than average courses of treatment.

In most instances some evidence of activity, if only increased sedimentation rate, occurs when cortisone or ACTH is stopped. Frequently this is a temporary phenomena often spoken of as rebound. It is difficult to be sure in any given case whether the signs of activity will subside or progress. It has been our practice to reinstitute hormone treatment when cardiac findings deteriorate, when joint pains or fever last more than two days, or when the sedimentation rate is definitely abnormal and still rising in the second week after hormone was stopped. Repeat courses of hormone, usually shorter than the original, have been administered to fifteen patients.

Because of the difficulty of drawing the line between relapse and rebound we have not tabulated the number of relapses.

Long-Continued Low-Grade Activity.—Seven patients have maintained high sedimentation rates for months without symptoms. Some of these have evidence of increased cardiac damage.

COMPARISON WITH SALICYLATE THERAPY

Lacking a valid control group during the period for hormone therapy, we have reviewed our records of the period from December, 1946, to April, 1950, for comparison. The rheumatic admissions during that

period were about the same in number and severity as the 1950 to 1953 group.

TABLE IV. PRECORTISONE GROUP

TOTAL PATIENTS	VALVULAR LESIONS	CARDIAC ENLARGEMENT	DECOMPENSATION
240	105 (41%)	53 (22%)	28 (12%)

These patients, if active, were treated with salicylates, usually aspirin, ¾ grain per pound per day during the acute stages of their attacks. The nonspecific supportive measures and follow-up care were largely the same as for the hormone-treated patients. Sulfadiazine was used for prophylaxis.

CHANGES IN HEART SIZE

It was not practical to compare the results of change in heart size in a definite way because x-ray films were not obtained at the same time intervals in the two groups. It is our impression that there is no great difference between the two groups in this respect. The phenomenon of increase in heart size with clinical improvement in the patient was not observed in the salicylate-treated patients.

DEATHS

Table V shows the number of deaths from rheumatic fever in Children's Hospital of Michigan for the control period as compared with the number occurring in the period of this study. Of the five untreated patients who died in the later group, one patient was admitted in April, 1950, at a time when no ACTH or cortisone was available to us. It is possible that this child would have benefited by cortisone or ACTH treatment. Three

TABLE V. DEATHS

	PATIENTS	DEATHS
Control Period	240	15
Hormone Period	255	8 (Hormone treated, 3 Nonhormone treated, 5)

were admitted in extreme failure after prolonged illness and the fifth died, a few hours after admission, of rheumatic pneumonia and myocarditis, diagnosed at autopsy. The total number of deaths during the period when hormone therapy was available was about half that of the prehormone period. This is very suggestive, but not statistically significant in a group of this size.

There were no cases of subacute bacterial endocarditis in either group. Patients with subacute bacterial endocarditis at the time of first admission have been excluded.

REVERSAL OF APPARENT VALVULAR LESIONS

In Table VI we have listed the number of patients in the precortisone period and of the hormone-treated group who were admitted within two months of the onset of their first attack and who had physical signs of

TABLE VI. DISAPPEARANCE OF PHYSICAL SIGNS OF VALVULAR LESIONS
(First attacks, less than two months' duration)

	NO. PATIENTS	REVERSAL
Prehormone	38	3
Hormone treated	38	20

valvular lesions. The number of patients in each group who lost such signs is shown. For the hormone-treated cases this refers to permanent disappearance of murmurs while under treatment; for the control

group, disappearance within six months. In both groups there have been additional cases of late disappearance of murmurs, two years or more after the attack.

Of the twenty hormone-treated patients, referred to in Table VI, whose signs of valvular lesions disappeared, only three were among our first forty-four cases. Less severity and earlier and more intensive therapy for the later patients as compared with the earlier ones probably account for this disparity.

DISCUSSION

The disadvantages of comparing a group of patients treated during one period of time with an earlier group are many. Factors other than those under consideration may have influenced the results, and the interpretation of earlier records is more difficult than those of recent cases fresh in the mind. There is no doubt that because we were using new and potent substances we watched the hormone-treated patients more meticulously than was sometimes true in the past. The time spent in the hospital proper has been longer in general for the hormone-treated patients than for those of the earlier period. On the other hand, the time spent in the convalescent home has often been less for the recent patient. Nevertheless the handling of the two groups was similar and we believe that the use of cortisone and ACTH was responsible for the differences in results.

It is obvious that cortisone does not cure rheumatic fever. We use it in the hope of suppressing the inflammatory reactions which occur during rheumatic activity. If this can be done without interfering with the patient's natural tendency to recover and without undue danger from the drug itself, one might expect to lessen the damage from the attack in question. In some patients rheumatic fever pursues a low-grade course of long duration. In such cases long-term use of the hormones might do more harm than good. In subacute as well as acute rheumatic fever, with the precautions we have taken, the dangers inherent in the use of cortisone and ACTH are not great in relation to the seriousness of the disease.

So far as we can judge, the administration of these hormones does not interfere with natural recovery from attacks of rheumatic fever. Whether or not the total duration of individual attacks is changed is a problem beyond the scope of this report. This point would be extremely difficult to prove because of the variability of the disease, the chronicity of many cases, and the indefinite end point of low-grade activity.

SUMMARY

The results of cortisone and ACTH therapy in 122 closely followed cases of active rheumatic fever with carditis have been presented.

The number of deaths occurring among all rheumatic fever admissions during the period of availability of hormone for therapy has been less than among a similar earlier group.

The incidence of reversal of signs of valvular lesions in first attacks of hormone-treated patients has been greater than that of the prehormone period.

Our criteria for the selection of cases for cortisone or ACTH therapy,

the dosage, duration of treatment, and the precautions taken have been stated. We administer these substances only to closely supervised hospitalized patients in whom we can demonstrate active carditis.

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GROWTH AND DEVELOPMENT OF NEGRO INFANTS

VI. Relationship of Certain Environmental Factors to Neuromuscular Development During the First Year of Life

Angella D. Ferguson, M.D., Fred F. Cutter, A.M., and Roland B. Scott, M.D.
Washington, D. C.

IN A previous communication,[1] we reported the time of occurrence of twelve neuromuscular patterns of behavior in the development of two groups of Negro infants from different socioeconomic backgrounds during the first year of life. The neuromuscular steps studied were smiling, vocalization, head control, hand control, rolling, sitting, crawling, prehension, pulling up, walking with support, standing alone, and walking alone. Briefly, the infants from a low socioeconomic group when compared with a group of infants from private practice showed definite motor acceleration from the eighth to the thirty-fifth week of life, after which the development of the two groups was essentially the same. Also, the neuromuscular development of the total Negro sample in general was more accelerated than that reported by several observers for white infants.[2-4]

Other studies have also indicated precocious development of Negro infants during the first year of life when compared with American white infants. Curti and associates[5] studied the maturation of Negro infants in the British West Indies in terms of the Gesell developmental schedules and reported that the Negro infants were "precocious" in the time of creeping, standing, and walking in comparison with the New Haven white infant. Pasamanick[6] observed, in a study of the development of New Haven white and Negro infants, that the Negro infant was "fully equal in behavioral development to the average New Haven white baby." Contrariwise, McGraw[7] reported in 1931 that the performance of young Negro infants on various developmental tests was inferior to that of the white infants studied.

The purpose of this report is to analyze certain environmental and cultural factors and to determine, if possible, the influence and relationship of these factors to the neuromotor development of Negro infants during the first year of life.

METHOD

The procedure involving the neuromuscular development of 708 healthy, full-term Negro infants from different socioeconomic classes during the first year of life was presented in a previous report.[1] One category consisted of 511 subjects from free well-baby clinics and were designated as a low income group. A second group of 197 infants were observed in a private pediatric practice and were designated as a middle in-

From the Department of Pediatrics of Howard University College of Medicine and the Pediatric Service of Freedmen's Hospital.

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come group. All the subjects were from the Washington, D. C., metropolitan area.

On the first visit to the physician, the following data were obtained: sex of the child, birth weight, number of siblings, annual family income, and the education and occupation of the parents. On subsequent visits to the observer, the development of the infant was appraised through the twelve neuromuscular patterns. Approximately 250 or more observations were made in each developmental category. The socioeconomic data of our subjects were tabulated and analyzed in relationship to the observed growth pattern. All of the data collected during the period of this investigation were used in compiling the tables presented here.

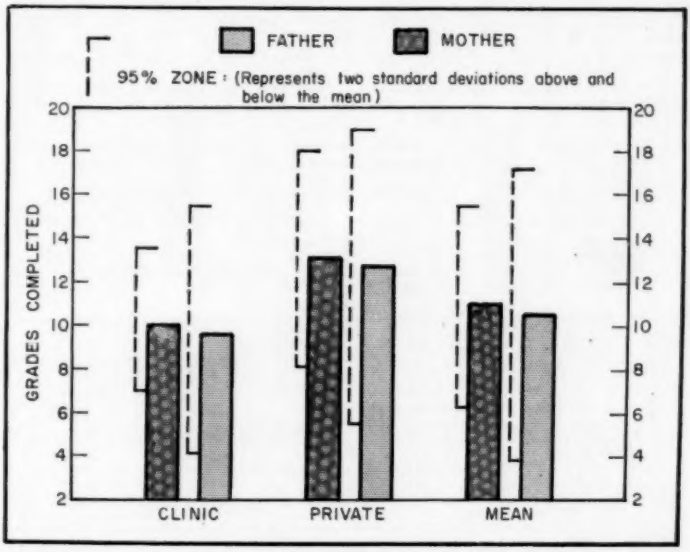

Fig. 1.—Formal education received by the parents of infants from two study groups. The education of the mothers was more advanced than that of the fathers in both groups.

RESULTS AND COMMENT

In comparing the two study groups of Negro infants, certain interesting differences were revealed. The average annual family income of the middle and low socioeconomic groups was $4,314.00 and $2,324.00, respectively. The parents of the infants from private practice averaged three years more formal academic education than the parents of our clinic infants; however, there were many exceptions in both groups (Fig. 1). The education of the mothers was more advanced than that of the fathers in all groups, but these differences were not statistically significant.

Table I shows the average number of siblings per family for the two groups studied. There was an inverse relationship between the number of children and the academic education of the mother (Table II).* On the

*A statistical measure of the degree of association between the number of siblings and education of the mothers is given by a chi square of 36.65 with six degrees of freedom. This is significant at the 1 per cent level. A contingency coefficient (an approximation of the correlation coefficient) calculated on the basis of this chi square is 0.33.

basis of our sample, there was no relationship between the number of siblings and average age of "walking alone." Similarly, the formal academic education of the mother and the average age of "walking alone" were not significantly statistically related (Table III).

TABLE I. NUMBER OF SIBLINGS PER FAMILY OF THE TWO GROUPS OF SUBJECTS USED IN THIS STUDY

	CLINIC	PRIVATE	TOTAL
Number of subjects	511	197	708
Mean number of siblings	1.75	.58	1.43
S.D.*	1.99	.91	1.84

*Standard deviation.

alone" (mean age 50 weeks), there was no significant difference between the weight of the two socioeconomic groups. At both developmental periods, the males weighed more than the females.

TABLE II. A SIGNIFICANT DEGREE OF ASSOCIATION EXISTS BETWEEN THE NUMBER OF SIBLINGS AND THE EDUCATION OF THE MOTHER, IN AN INVERSE MANNER, I.E., THE MORE EDUCATION THE MOTHER HAS ACQUIRED, THE FEWER NUMBER OF SIBLINGS

NO. OF SIBLINGS	EDUCATION OF MOTHERS			
	≤ 9TH GRADE	10TH-12TH GRADE	≥ 13TH GRADE	Σ
0	16	66	60	142
1	15	26	25	66
2	12	17	10	39
3+	20	24	2	46
Σ	63	133	97	293

TABLE III. RELATIONSHIP OF THE MOTHER'S EDUCATION, NUMBER OF SIBLINGS, AND THE MEAN AGE OF "WALKING ALONE"

	EDUCATION OF THE MOTHER		
	≤ 9TH GRADE	10TH-12TH GRADE	≥ 13TH GRADE
Number	63	133	97
Mean* in weeks	50.8	48.0	49.2
Standard deviation	5.6	13.2	7.0

ANALYSIS OF VARIANCE

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	VARIANCE ESTIMATE
Total	29.339	292	—
Between	325	2	162
Within	29.014	289	100

F = 1.62 Not significant

	NUMBER OF SIBLINGS			
	0	1	2	3+
Number	145	67	41	46
Σx	7188	3362	2057	2347
Mean* in weeks	49.6	50.2	50.2	51.0
Standard deviation	6.5	7.0	5.8	6.9

ANALYSIS OF VARIANCE

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	VARIANCE ESTIMATE
Total	13510	298	—
Between	77	3	25.7
Within	13433	295	45.5

F = 1.77 Not significant

*Mean age in weeks.

In order to determine the effect of weight upon motor development, the weights at two representative periods, namely, "sitting" and "walking alone," were analyzed. As can be seen from Fig. 2, the infants from private practice had a significantly higher weight when compared with the clinic infants at the developmental period of "sitting" (mean age 25 weeks). Subsequently, this discrepancy in weight tended to become less pronounced to a point where, at the age of "walking

The higher weights for the private infants at the age of "sitting" probably is a reflection of several factors, namely:

1. The higher initial birth weights of the private infants.

2. The dominant interest in feeding on the part of the mothers at this age period (6 to 9 months).

3. This is a period of rapid growth and, if the economic status of the family permits overfeeding, there is a tendency to obesity.

At the age of "walking alone," there is a natural tendency toward a relative deceleration in growth rate and also a new interest in exploring the environment with the resultant intake of less food on the part of the infant. These factors, no doubt, play a part in the similarity in weight of the two groups at this age period.

The finding of an inverse ratio between weight and motor development is confirmed by the relationship of weight and age of "walking alone." These variables were studied statistically by an analysis of variance technique (Table IV) and found to be significantly related. Thus, generally, the greater the weight of the infants,

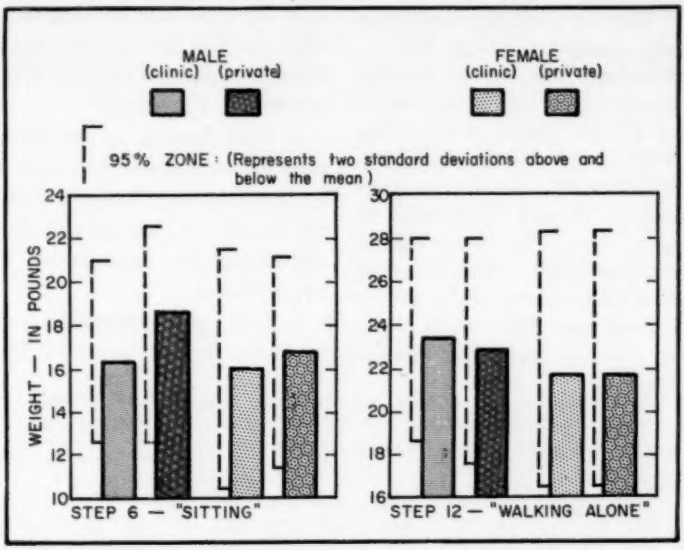

Fig. 2.—Comparison of weight for male and female infants from two groups at the mean age of "sitting" and "walking alone." Although the private infants had a significant superiority in weight at the mean age of "sitting," there was no significant difference between the two groups at the mean age of "walking alone." At both periods, the males weighed more than the females.

TABLE IV. RELATIONSHIP OF WEIGHT TO MEAN AGE OF "WALKING ALONE"

In general, the greater the weight of the infant the later he tended to walk alone

	MALES			FEMALES		
Weight	< 20 LB. 15 OZ.	21 LB. 0 → 24 LB. 15 OZ.	> 25 LB. 0	< 20 LB. 15 OZ.	21 LB. 0 → 24 LB. 15 OZ.	> 25 LB. 0
Number	31	80	31	28	78	19
Mean	47.6	49.8	54.1	46.8	50.6	50.0
	S.S.*	DoF*	V. ESTIM.*	S.S.	DoF	V. ESTIM.
Total	6,408	141	—	4,260	124	—
Between	.700	2	350	305	2	152
Within	5,708	139	41.1	3,955	122	32.4
	$F = \frac{350}{41.1} = 8.52$: Significant at 1% level			$F = \frac{152.5}{32.4} = 4.71$: Significant at 1% level		

*S.S., Sum of squares; DoF, degree of freedom; V. Estim., variance estimate.

the later they tended to walk alone (Table IV). The height of our infants was tabulated and compared by source for the two study groups at steps 6 ("sitting") and 12 ("walking alone"). None of the differences were statistically significant (Table V).

Thirty infants selected at random from private practice were tested, using the Cattell Infant Scale. The infants were tested shortly after they had learned to walk alone, i.e., between approximately 10 and 14 months of chronological age. The mean I.Q. of the sample was 108. Similarly, the mean age of achievement of the ability to walk alone was 47.5 weeks. We concluded that our sample of apparently normal children did not show any relationship between measured intelligence and the age of "walking alone."*

TABLE V. COMPARISON OF THE HEIGHTS OF MALE AND FEMALE INFANTS FROM THE TWO STUDY GROUPS AT THE MEAN AGE OF "SITTING" AND "WALKING ALONE"

	STEP 6—"SITTING"							STEP 12—"WALKING ALONE"						
	CLINIC			PRIVATE				CLINIC			PRIVATE			
	N*	M†	S.D.‡	N	M	S.D.	COMPARISON	N	M	S.D.	N	M	S.D.	COMPARISON
Males	26	25.9	1.3	30	25.9	4.8	$Z^{**} = 0$	25	29.8	2.1	65	28.9	4.5	$Z^{**} = 1.3$
Females	31	25.6	1.7	31	25.7	1.5	$Z^{**} = .33$	21	29.8	1.6	62	29.8	2.9	$Z^{**} = 1.93$

*Number of subjects.
†Mean.
‡Standard deviation.
**$Z = 1.96$ is required for significance at the 5 per cent level.

SUMMARY

The neuromuscular development during the first year of life of Negro infants from low and middle socioeconomic levels was studied and related to certain environmental and cultural factors. The study groups differed in annual family income, type of occupation, and the amount of education achieved by the parents.

An analysis of the data shows:

1. That an inverse relationship exists between the number of siblings and the education of the parents.

2. That the age of "walking alone" apparently is not affected by the number of siblings and the formal academic education of the mother.

3. That there is an inverse relationship between the weight gain and the achievement of "sitting" and "walking alone," i.e., the greater the weight the slower the development of these two patterns.

4. That no relationship exists between intelligence (at about 13 months of age, measured by the Cattell Infant Scale) and the age of "walking alone" in a sample of normal infants.

Acknowledgment is made to Dr. Ella Oppenheimer, Director of the Bureau of Maternal and Child Welfare, and Dr. K. G. Symmonds, Attending Physician of the Bureau of Maternal and Child Welfare, who assisted in furnishing a portion of the clinic infants used in this study, and to Dr. Melvin E. Jenkins, Clinical Instructor in the Department of Pediatrics, Howard University College of Medicine, who assisted in the collection of the data for this report.

*The rank order correlation index was found to be 0.251 which is not significant with this number of cases. Likewise, an analysis of variance of the same data with I.Q. trichotomized was also negative.

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A Statistical Prognosis

We hear there is a very remarkable boy, or young giant, now living in the town of Hingham, where he was born in the year 1758; his name is Israel Remmington, and his amazing size, for a person of his age, as well as strange features, has attracted the attention of multitudes; he is about 5 feet in height, is remarkably strong, and weighs upward of 200 weight, has five fingers and a thumb on each hand, and six toes on each foot. It is thought if he should continue to increase in height and size at such an amazing rate, as he has within these few years, he will be 10 feet high, and weigh 4 or 500 weight by the time he is 21 years old. It is said he is expected in town in a few days.

FROM MASSACHUSETTS GAZETTE & BOSTON WEEKLY NEWS-LETTER, Dec. 10, 1772.

THE USE OF METHAPYRILENE HYDROCHLORIDE AS A SEDATIVE AND SOMNIFACIENT AGENT

RALPH N. SHAPIRO, M.D.
NEWARK, N. J.

IN PEDIATRIC practice there is need for a sedative and somnifacient medication. A large group of children have psychomotor tension which manifests itself in irritability, crying, "colic," and insomnia. Parent problems, frequently oversolicitude, may lead to neuropathic behavior in children. The child presents the picture of irritability and restlessness by day and sleeplessness by night. The overactivity and inability to sleep lead to physical and mental exhaustion which interferes with normal healthy development.

The traditional sedatives and somnifacients, barbiturates or chloral hydrate, are not always satisfactory in these cases. For this reason, we explored the use in children of methapyrilene hydrochloride.* This preparation is well tolerated and does not have dangers of habit formation.[1] Its safety was ascertained[1] in a group of children ranging in age from 5 months to 12 years who received the drug in adequate dosage over a four-week period without exerting adverse effects upon the hemopoietic system or urine.

From previous acute toxicity tests by Roth and associates[2] in mice it can be calculated that the LD_{50} of methapyrilene hydrochloride upon oral administration is 198 mg. per kilogram. Upon intraperitoneal and intravenous injection the LD_{50} is 90 mg. per kilogram and 14 mg. per kilogram, respectively. In the guinea pig the LD_{50} (oral) is 233 mg. per kilogram. The dosage schedule we followed in our clinical investigation called for up to four doses per day, containing a total of from 1/40 to 1/200 of these LD_{50} doses of methapyrilene hydrochloride. Frequently a single dose per day sufficed to induce sleep or sedation.

The mechanism by which methapyrilene exerts its somnifacient effect has been investigated in man by Roback and co-workers.[3] They found that it lowers the flicker fusion threshold, which is an indication that it acts by depression of the central nervous system.

SELECTION OF PATIENTS

Thirty-three children from 4 weeks to 12 years old who suffered from sleep disturbances, irritability, hyperactivity, restlessness, "colic," and jactatio capitis nocturna were treated. This group included one 11-year-old girl with a tentative diagnosis of chorea and a 12-year-old child exhibiting a nervous tic. Treatment lasted from one to sixty-six days.

*Lullamin drops were generously supplied to us by Dr. Bernard J. Brent of Reed & Carnrick, Jersey City, N. J.

DOSAGE SCHEDULE

The doses used were based upon the age of the children, essentially according to the following schedule:

Children	
Under 1 yr.	0.2-0.4 c.c.
From 1-6 yr.	0.6 c.c.
From 6-12 yr.	0.8 c.c.
Over 12 yr.	1.2 c.c.
Adults	1.6 c.c.

These doses were given orally, undiluted or mixed with milk or orange juice, one to four times per day as needed and were measured with a calibrated medicine dropper.

RESULTS OF THERAPY

Out of thirty-one children exhibiting sleep difficulties or requiring daytime sedation, twenty-four responded well to the therapy as indicated in Table I; nine of these responded satisfactorily even though their dose was slightly below that of the above schedule. In an earlier group not included in this report and treated with approximately one-half the above dose schedule, the percentage of favorable results was decidedly lower. The therapy was effective in one child only during the first but not during the second week, while another child showed only a slight improvement in his sleep pattern.

A single daily dose sufficed in sixteen of the twenty-four successfully treated children. A second dose was given to the other eight children of this group, usually a few hours after the first dose to obtain the desired results.

Most of the children fell asleep from one-fourth to one-half hour after their first or second dose. The sleep that ensued was a peaceful one as judged by the expression of the face and the relaxed positions. Five children did not respond to the treatment. One of these, however, received only one-third of the dose now recommended and the child shares the bedroom with the parents and another child. One child, who became nauseated and therefore was not continued on this regimen, is listed as a failure. During periods of pain, such as teething, the treatment was not always effective. Sleep lasted usually all night except for an awakening for feeding or for visiting the bathroom.

Those children who used to bang their heads into pillows either stopped this habit or did it only rarely. One of these started singing himself to sleep. In general, the infants smiled more during daytime and the older children were happier, probably partly because of improved rest at night. One patient with a nervous tic improved considerably and showed only an occasional tic when the medication was withheld after a twelve-day period of treatment.

No untoward effects were noticed in any of the children treated over periods of time of up to sixty-six days.

When the medication was discontinued the children had adopted a regular sleep pattern and continued to fall asleep normally and be more relaxed during daytime. No withdrawal symptoms were ever encountered.

SUMMARY

Methapyrilene was given to children from 4 weeks to 12 years of age for from one to sixty-six days for induction of sleep. Sleep was induced and relaxation of hyperactive states during daytime was achieved in twenty-four of thirty-one of the children. The time that elapsed between the administration of the medication and onset of sleep was from one-fourth to one-half hour. The children slept in

TABLE I. SUMMARY OF CASE RESULTS

INITIALS	SEX	AGE	DIAGNOSIS	RC 503 DOSES (C.C.)	RC 503 TOTAL DOSE PER DAY (C.C.)	RC 503 DURATION OF R (DAYS)	RESULTS TIME BETWEEN R AND ONSET OF SLEEP (MIN.)	RESULTS DURATION OF SLEEP	REMARKS
J. A.	F	4 wk.		0.2	0.4	53	20	8½ hr.	Sleeps at much longer intervals. 3½ to 5 hr. Extremities relaxed. Expelling much flatus. Smiles, appears much happier
D. R.	F	7 wk.	Hyperactive colic	0.2 +0.2	0.4	26			No effect
E. P.	F	10 wk.	Hyperactive colic	0.4	0.4	66	10	10-13 hr.	Continued good sleep pattern. No daytime nap
M. M.	F	4 mo.	Restless sleeper	0.4	0.4	5		8 hr. until feeding time	More restful sleeping, at much longer intervals
R. C.	F	4 mo.		0.3	0.3	29		11 hr.	Slept well with one waking for feeding
P. C.	F	4 mo.		0.3	0.3	29	10-20	5-6 hr.	Better sleep, more relaxed. Expelling flatus
C.	F	7 mo.		0.4	0.4	17	10	9 hr.	Excellent results first week, no results second week
N.	M	8 mo.	Hyperactive	0.2 0.4	0.2 0.4	17			No effect
S.	M	10 mo.		0.3	0.3	12	15	All night	Sleeps all night
S. J.	M	10 mo.		0.2 0.2 0.8	0.4 0.8	3 11			No effect No effect
A. C.	F	11 mo.		0.3	0.3	17	10-20	9-10 hr.	Four to five nights' good rest. Other nights very poor; teething
A. B.	M	2 yr.		0.4	0.4	23	15	10 hr.	Increased relaxation. Much happier disposition. Banging of head decreasing. Child now sings himself to sleep
S. H.	F	2 yr.		0.8	0.8	11	20	4-6 hr.	Improvement in sleep pattern
W. F.	M	2 yr.		0.2 +0.2	0.4	5			Mother reports child worse
E. M.	F	3 yr.		0.4	0.4	9	10-20	10½ hr.	Great improvement
P.	F	3 yr.		0.4	0.4	23	15	10 hr.	Better sleeper, happier baby
G. L.	F	11 yr.	Extreme twitching of head and shoulders (chorea?)	0.4 b.i.d. 0.6 b.i.d. 0.6 t.i.d. 0.8 t.i.d.	0.8 1.2 1.8 2.4	7 7 7 21			Twitching lessened Progressive relaxation and lessening of twitching Twitching hardly noticeable Twitch rare and very slight
B.	F	12 yr.	Nervous tic Wheeze	0.2 t.i.d.	0.6	12	30	9-10 hr.	Tic diminished considerably

relaxed positions. No withdrawal symptoms were encountered upon discontinuation of therapy and the normal sleep pattern continued which had been acquired during the period of medication. Except for one child who became nauseated, methapyrilene was well tolerated and well accepted, and there was no evidence of habit formation.

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Accidents Due to Pride

About ten Days ago, a Child near two Years old, in this Town, being left with another Child something older, going too near the Fire, its Cloaths took Fire, and before any Help came, the poor Child was so terribly burnt, that it died the next Day. One would think, the frequent Accidents of the Sort, should cure Mothers of their senseless Pride, in dressing their Infants in Chints or Callico, which are the most Susceptible of Fire of any Sort of Cloathing. But if they will risque their Children's Lives for the sake of a fine Rag, they ought at least to take a little more care of them.

FROM BOSTON EVENING POST, January 30, 1749.

B. F 12 yr. Nervous tic (choreaf) Whoose 0.2 t.i.d. 0.6 12 30 9-10 hr. Tic diminished considerably

TREATMENT OF CHILDREN WITH ACUTE STREPTOCOCCAL PHARYNGITIS WITH A SINGLE PENICILLIN DOSE

HANS HARTENSTEIN, M.D., AND HARRY A. FELDMAN, M.D.
SYRACUSE, N. Y.

THE importance of early and adequate treatment of group A streptococcal infections in the prevention of both acute rheumatic fever and glomerulonephritis has been illustrated repeatedly during recent years.[1-3] Penicillin is believed to be the drug of choice in this respect for it rapidly and effectively inhibits the reproduction of the organisms and, if continued for a sufficient period of time, reduces antibody formation.[4-6]

This report is concerned with the results obtained in the treatment of twelve children with acute pharyngitis by means of a single dose repository penicillin product* which contains 600,000 units of benzathine penicillin G, 300,000 units of procaine penicillin G, and 300,000 units of buffered potassium penicillin G. The 1,200,000 units of this penicillin mixture is in an aqueous suspension of 2 ml. volume and administered as an intramuscular injection. Each patient received one such injection as treatment for the pharyngitis.

MATERIAL AND METHODS

The twelve children included in this study were patients of the pediatric out-patient clinic of the Syracuse Dispensary. Their ages ranged from 3 to 11 years and included eight girls and four boys.

The clinical diagnoses and relevant bacteriological findings are summarized in Tables I and II. Serological identification of the streptococci was accomplished by the method of Swift and associates.[7]*

The patients presented themselves for diagnosis and therapy at various periods after the onset of their illnesses. None had either a history or evidence of previous rheumatic fever, rheumatic heart disease, or acute glomerulonephritis. Each patient had a urinalysis prior to treatment and on at least one subsequent occasion. Total leukocyte counts were performed initially and for the next two to four visits. Sera for determination of the antistreptolysin-0 content† were obtained at the first visit and on at least one subsequent occasion; most patients had two to three such determinations. Physical examinations and laboratory procedures, including throat cultures, were performed during a minimum of twenty-four and a maximum of 122 follow-up days.

RESULTS

In Table III is presented a detailed compilation of the initial physical and

From the State University of New York, Upstate Medical Center at Syracuse, New York, and the Kilian Research Laboratory, Wieting-Johnson Hospital for Rheumatic Diseases.

Supported by a grant from the Masonic Foundation for Medical Research and Human Welfare.

*Panbiotic, supplied by Bristol Laboratories, Inc., Syracuse, N. Y.

*We are indebted to Mr. Kenzo Kuroda for the typings.

†These tests[8] were performed by Miss Anne L. Gillen to whom we express our thanks.

laboratory findings as well as the follow-up data. One patient (L. S.), with both nose and throat cultures positive for group A streptococci, was found to have negative cultures twenty-four hours after the administration of Panbiotic. Two patients (W. S. and G. S.), with positive nose and throat cultures, had negative cultures when re-examined seventy-two hours later, and two other patients' cultures (B. S. and L. P.) had become found to have negative cultures. Neither of the two patients (E. S. and M. L.) whose initial nose and throat cultures were negative for group A streptococci was ever found to have a positive culture throughout the period of observation. In no instance did a nose culture become positive after the throat culture had become negative.

Among six patients there was no significant rise in antistreptolysin-0 noted during the period of observation.

TABLE I. RELATION OF CLINICAL TO BACTERIOLOGICAL FINDINGS AMONG TWELVE PATIENTS WITH PHARYNGITIS

DIAGNOSIS	CULTURES			
	THROAT		NOSE	
	POS.*	NEG.	POS.	NEG.
Acute pharyngitis, exudative tonsillitis	6	1†	5	2
Acute pharyngitis, exudative tonsillitis not noted	4‡	1	1	4
Total	10	2	6	6

*Group A streptococci present.
†Group B streptococci present.
‡One of these four patients, additionally, had purulent otitis media due to group A streptococci (nontypable).

TABLE II. STREPTOCOCCAL TYPES IDENTIFIED AMONG 12 PATIENTS WITH PHARYNGITIS

NO. CASES	STREPTOCOCCAL TYPE ISOLATED	
3	Group A	6
1	Group A	19
2	Group A	41
1	Group A	42
1	Group A	43
2	Group A	Nontypable
2	Nongroup A	

negative when recultured ninety-six hours after treatment.

Of the patients with positive initial throat and negative nose cultures, one (M. V.) was seen forty-eight hours after the mixture of penicillin had been administered and had a negative culture at that time; one (P. S.) was re-examined seventy-two hours later and had a negative culture; two children (M. G. and Edw. S.) were seen after ninety-six hours and another (C. L.) after seven days and were

Changes in antistreptolysin-0 titers bordering on the significant were detected in the remaining six patients. In all of these, respiratory disease symptoms had been present for a "few days" in one, to one, two, three weeks, or one month in the others. The antibody changes probably had been initiated prior to therapy either by the present or an antecedent streptococcal infection.

All patients with symptoms felt better within one to two days and

TABLE III. SUMMARY OF CLINICAL AND LABORATORY FINDINGS NOTED BEFORE

PATIENT	AGE IN YEARS	SEX	PRIOR TO TREATMENT: ONSET OF SYMPTOMS	SORE THROAT	EXUD.	TEMP. ° F.	LYMPH NODES	WBC	URINE	CULTURES: T	CULTURES: N	AS-O TITER
M. V.	3	F	2 wk.	2+	0*	99.8	2+	18,200	0	A-N.T.†	0	200
M. G.	8½	M	‡	1+	0	98.6	2+	9,900	0	A-43	0	500
L. S.	6	F	1 wk.	2+	2+	101.2	2+	25,300	Tr. alb. 10-200 WBC	A-41	A-41	500
E. S.	9½	F	2 da.	1+	1+	100.2	3+	N. D.	4-6 WBC	0	0	200
B. S.	6	F	1 mo.	2+	1+	103.4	3+	13,600	Tr. alb.	A-41	A-41	125
Edw. S.	4	M	"Few days"	0	0	99.2	2+	11,600	0	A-42	0	250
M. L.	4	F	2 wk.	2+	3+	103.0	4+	19,600	0	B	0	400
C. L.	11	M	4 da.	2+	2+	102.6	3+	16,300	0	A-6	0	1,250
W. S.	4	M	2 da.	3+	3+	100.6	3+	17,200	0	A-N.T.	A-N.T.	625
L. P.	10	F	2 wk.	4+	4+	101.0	4+	23,350	0	A-19	A-19	1,585
P. S.	3	F	3 wk.	1+	2+	—	2+	14,400	0	A-6	0	400
G. S.	3	F	1 da.	1+	0	—	3+	12,000	0	A-6	A-6	1,000

*Normal or negative (normal WBC = under 10,000.)
†Group A, nontypable.
‡Normal on first day after treatment begun.
AS-O TITERS:
$\frac{500}{45}$ = 500 units 45 days after treatment was instituted (this method of recording is used throughout Table.

throats usually appeared normal within three days. No bacteriological relapses occurred after a minimum of twenty-four days and a maximum of 122 days. Reinfection with group A streptococci of a different type occurred in one patient (W. S.) thirty-nine days after Panbiotic had been administered. At this time, a sibling was found to have acute exudative tonsillitis due to this newly acquired type of streptococcus.

No allergic reactions to penicillin were observed during this study. All patients developed slight induration and tenderness at the site of injection which disappeared completely within a maximum of one week.

Neither acute rheumatic fever nor acute glomerulonephritis was noted in

AND AFTER TREATMENT AMONG TWELVE PATIENTS WITH PHARYNGITIS

FOLLOWING TREATMENT											
SORE THROAT	EXUD.	TEMP.	LYMPH NODES	WBC	URINE	CULTURES T	CULTURES N	AS-O TITERS		NO. DAYS WITHOUT RELAPSE OR RECURRENCE	REMARKS
0‡	0	0	0	0	0	0	0	500	625	65	A-N.T. isolated from draining ear; discharge cleared in 4 da.; culture negative in 2 da.
1		1	2	2	14, 39	2		39	65		
0	0	0	0	0	0	0	0	400	400	58	
4			8		8, 43	4		12	40		
0	0	0	0	0	0	0	0	625	833	69	
1	5	1	13	7	13, 20	1	1	13	20		
								500			
								35			
0	0	0	0	0	0	0	0	250	150		Yeast vaginitis present throughout study
5	5	5	10		19, 32			19	32	68	
0	0	0	0	0	0	0	0	317	250		
4	4	4	12	4	6, 12, 19	4	4	19	32	32	
0	0	0	0	0	0	0	0	400	500		
			14	3	14	4		14	27	67	
0	0	0	0	0	0	0	0	625	400		
5	4	4	11	11	11	11		11	18	45	
								500			
								45			
0	0	0	0	0	0	0	0	625	500	122	
4	7	9	9	7	17, 21	7		17	21		
								400	400		
								46	73		
0	0	0	0	13,300	0	0	0	833	833	32	Infection with A-6 after 39 da. (sibling found to have same type)
7	7	3	11	3	28	3	3	28	60		
								833			
								91			
0	0	0	0	13,200	0	0	0	1,000		26	
12	12	3	12	3	26	4	4	12			
0	0	0	0	0	0	0	0	1,000		24	
3	4		11	11	11	3		24			
0			0	0	0	0	0	833		24	
3	0	0	11	24	11	3	3	24			

any patient during the period of observation.

COMMENT

The efficacy of the penicillin mixture used in this study has previously been demonstrated in a series of young adults with streptococcal pharyngitis.[9] Successful results with the same product have been reported in the treatment of syphilis, yaws, pinta, and in one case of actinomycosis.[10] There have been several reports in which one injection of benzathine penicillin G was administered successfully in the treatment of purulent otitis media in children,[11] streptococcic pharyngitis,[12] and various beta hemolytic streptococcal diseases in children.[13, 14] Benzathine penicillin G as a single injection at monthly intervals also has been used successfully for the prophylaxis of rheumatic fever.[15, 16]

In the present study Panbiotic effectively prevented bacteriological relapses, probably because of its benzathine penicillin content; it satisfactorily and speedily controlled the clinical manifestations of streptococcal

disease. Of considerable advantage was the fact that only one injection was necessary to cure the infection which is especially important when dealing with children.

SUMMARY AND CONCLUSIONS

Twelve children with acute upper respiratory tract disease, in ten of whom it was proved to be due to group A streptococci, were treated with one intramuscular injection of Panbiotic, a mixture of rapidly and slowly absorbed penicillins. Clinical and bacteriological remissions were prompt and without relapses. None of the patients developed subsequent acute rheumatic fever or acute glomerulonephritis. There were no untoward effects due to the drug except for mild tenderness and induration at the site of injection.

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THE OCCURRENCE OF CONVULSIONS IN CHILDREN WITH SHIGELLA GASTROENTERITIS

WILLIAM D. DONALD, M.D., CHARLES H. WINKLER, JR., PH.D., AND L. M. BARGERON, JR., M.D.
BIRMINGHAM, ALA.

DURING the course of clinical and bacteriological investigations on infants and children with diarrhea or dysentery, convulsions were observed in a number of the patients. Neurological manifestations in patients with bacillary dysentery are associated more frequently with infections caused by *Shigella dysenteriae* (Shiga) than by other members of the Shigella group. The Shiga bacillus is rarely encountered in the United States and was not found in this study. We wish to report the occurrence of convulsions in children with infections caused by *Sh. sonnei* and *Sh. flexneri*.

MATERIAL AND PROCEDURE

The patients included in this study were infants and children admitted to the pediatric service of the University Hospital over a twenty-month period. They constitute the majority of patients with diarrhea or dysentery during this period. Only those with diarrhea on whom the bacteriology was done by one of the authors were included in this report.

The routine bacteriologic work-up consisted of obtaining a rectal swab on each patient as soon as possible after admission, always before chemotherapy or antibiotics were started. The material from the rectal swab was then immediately inoculated by streaking on S-S (Shigella-Salmonella) agar and MacConkey agar. After twelve to twenty-four hours of incubation, the plates were examined, and suspicious colonies were transferred to Kligler iron agar. Those colonies on Kligler medium which showed a reaction typical of the Shigellae after twenty-four hours' incubation were tested with Shigella grouping antiserum (Lederle), using the macroscopic slide agglutination technique. In a number of instances it was possible to pick suspicious colorless colonies directly from the S-S or MacConkey agar plates and make a presumptive identification of the presence of a member of the Shigella group by the slide agglutination technic. Each culture that was isolated and found to agglutinate with one of the antisera was confirmed biochemically as belonging to the genus Shigella by the following reactions which characterize the group: the production of acid only in dextrose, failure to ferment salicin or utilize citrate, methyl red positive and Voges-Proskauer negative. Cultures identified as members of the Sonne group were slow lactose fermenters. Specific typing of the cultures was done by Dr. W. H. Ewing, in the Shigella Labora-

From the Departments of Pediatrics and Microbiology, Medical College of Alabama.

tory of the Communicable Disease Center at Chamblee, Georgia.

RESULTS

One hundred sixty-four patients with diarrhea were studied. The incidence of Shigella infections in these patients is shown in Table I. It will be noted that Shigella was isolated from sixty-four patients, giving an incidence of 39 per cent. This figure approaches those given by Cooper and associates[1] and Hardy and Watt.[2] *Sh. flexneri* was recovered from fifty-six patients and *Sh. sonnei* from eight. Of the 100 patients from whom Shigella was not isolated, a Salmonella was recovered from two children. No attempt to type any of the *Escherichia coli* was made in this group of patients. The incidence of convulsions in this group of patients according to age is recorded in Table II. Of the sixty-four patients with Shigella infections, twenty-nine had convulsions, giving an incidence of 45 per cent. This may be compared to an incidence of 12 per cent (twelve patients) in the group from whom Shigella was not isolated.

TABLE I. INCIDENCE OF SHIGELLA IN DIARRHEAL PATIENTS

	NUMBER OF PATIENTS		PER CENT
Positive for Shigella		64	39
Sh. flexneri	56		
Sh. sonnei	8		
Negative for Shigella		100	61
Total		164	100

TABLE II. INCIDENCE OF CONVULSIONS IN DIARRHEAL PATIENTS

	CULTURES POSITIVE FOR SHIGELLA			CULTURES NEGATIVE FOR SHIGELLA		
AGE	NO. PATIENTS	NO. WITH CONVULSIONS	PER CENT WITH CONVULSIONS	NO. PATIENTS	NO. WITH CONVULSIONS	PER CENT WITH CONVULSIONS
0-6 mo.	6	2		48	1	
6-12 mo.	12	0		23	3	
1-2 yr.	15	9		11	3	
2-5 yr.	23	15		15	5	
6-12 yr.	8	3		3	0	
Total	64	29	45	100	12	12

TABLE III. INCIDENCE OF CONVULSIONS WITH RELATION TO TYPE OF SHIGELLA ISOLATED

TYPE	NO. OF PATIENTS	PATIENTS WITH CONVULSIONS
Flexner 2a	18	10
Flexner 3	14	7
Flexner 4a	2	0
Flexner 6	13	4
Flexner y-like	1	0
Flexner not typed	8	4
Sonne	8	4
Total	64	29

The relationship of the occurrence of convulsions to the type of Shigella isolated is recorded in Table III. Convulsions were more frequent in those children who had infections caused by Flexner 2a and Flexner 3; however, the numbers are too small to draw any conclusions.

The charts of the two groups of patients were reviewed for a comparison of state of hydration, family history of convulsions, and a history of previous convulsions. There was no obvious difference in the state of hydration in the two groups and no correlation between the occurrence of convulsions and dehydration. A re-

view of the family history was positive in only one patient from each group, and only one patient in the entire series had a history of previous convulsions. A lumbar puncture was performed on eight patients with negative cultures, three because of convulsions and five because of drowsiness or temperature elevations which did not appear to be satisfactorily explained. All examinations of the spinal fluid from these patients were normal. Seventeen of the patients with Shigella infections who had convulsions had spinal fluid examinations, and no abnormal findings were noted. The serum electrolyte studies which were performed on both groups of patients were also reviewed, and no significant differences in the two groups either with or without convulsions were found. The maximum temperatures (rectal) of the patients in both groups and the relationship of convulsions is shown graphically in Fig. 1. As can be seen, a majority of the children who had convulsions had high temperatures.

Several of the children who had Shigella infections but did not have convulsions were noted to be disoriented and, as was noted by house officer, "about to convulse." These convulsions preceded the onset of the diarrhea in a number of cases, the child having his first foul, blood-streaked stool either in the emergency room or ward after being admitted because of the convulsion.

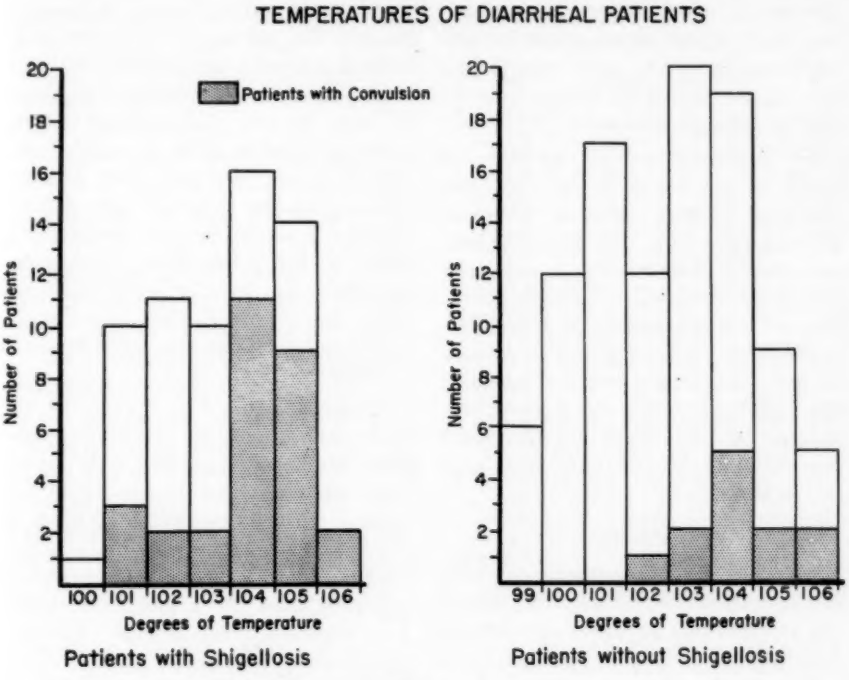

Fig. 1.

In two of the children, 5 and 6 months of age, who had convulsions and negative stool cultures, a diagnosis of cortical atrophy and subdural hygroma was made. No other neurological diagnoses were made in the remaining 162 patients.

Most of the patients were treated with sulfadiazine in addition to fluids, electrolytes, sedation, and supportive therapy. There were four deaths in the series. One 4½-year-old Negro male with a positive stool culture was admitted in shock with generalized convulsions and died within twenty-four hours after admission.

The 3 remaining deaths were in the group of patients with diarrhea who had negative stool cultures. One was a 7-week-old infant with *E. coli* septicemia, one a 1-month-old infant with pneumonia, and one a 7-month-old infant with severe neglect and diarrhea.

Although follow-up has not been adequate on this group of patients, there have been no recurrences of convulsions and no obvious neurological sequela in those who have been seen in the clinics.

DISCUSSION

It has been accepted generally that *Sh. dysenteriae* is the only member of the group which produces an exotoxin (neurotoxin). The production of a neurotoxin by this organism has been suggested repeatedly by clinical observations of patients with this infection.

Such a neurotoxin has not been demonstrated in association with the flexneri or sonnei organisms. Clinically, the occurrence of such a high incidence of convulsions in the group of patients here reported suggests the possibility that there may be a neurotoxin associated with these bacteria. A meningitic type of infection has been described previously in association with flexneri and sonnei infections. Felsen and associates[3] reporting on the New Jersey epidemic of 1934, found a meningitic type of infection in 13 per cent of 100 hospitalized patients. The symptoms exhibited included severe headaches, violent emesis, convulsions, and drowsiness or stupor. Convulsions actually occurred in 4 per cent of the patients. An interesting observation was that those with the meningitic type of infection had nasal or labial herpes, while none of the remaining patients exhibited such lesions. None of our patients had similar herpetic lesions. Denison and deHoll (1935),[4] in a clinical and bacteriologic study of thirty-five cases of Shigella infections in infants and children, make the comment that the "onset occasionally was accompanied by convulsions."

Kessel and associates[5] reported in 1936 that cases with Flexner infections often showed marked toxic symptoms accompanied by neurological reactions. Neter[6] in 1939 described a child with a Flexner infection who exhibited signs of marked meningeal irritation, and Block and co-workers[7] have reported a similar case. Blalock and Guthrie,[8] reporting on 215 cases investigated, comment on the toxic cerebral manifestations, especially with Flexner infections. They state that of the fifty-two patients on whom autopsy was performed there was often congestion and edema of the brain tissue and an increased subarachnoid fluid content. Cooke[9] in 1940 reported two cases of fulminating dysentery due to *Sh. sonnei* in which convulsions were a prominent part of the clinical pic-

ture. Hardy and Watt[10] in 1945 presented the largest series of patients with Shigella infections having convulsions as part of the clinical picture. They had 229 patients with infections classified as severe and 244 which fell within the mild group. Convulsions occurred in 11 and 10 per cent of the two classifications, respectively. Forbes[11] in 1954 reported an incidence of convulsions associated with shigellosis in 30 per cent of twenty children 1 to 2 years of age, 19 per cent of twenty-one children 2 to 5 years of age, and 18 per cent of eleven children 6 to 10 years of age.

Penner and Klein,[12] using a cross circulatory arrangement in dogs, concluded that following the intravenous injection of Shigella toxin the systemic effects are mediated through the central nervous system rather than by direct local action of the endotoxin.

The convulsions in the patients with Shigella infections reported here may have been simply febrile in nature. However, when compared with the group of patients from whom Shigella was not isolated, the incidence seems difficult to explain entirely on this basis.

SUMMARY

We are reporting a series of 164 infants and children with diarrhea or dysentery. A bacteriologic diagnosis of Shigella infections was made in sixty-four, or 39 per cent, of the patients. *Sh. flexneri* was isolated from fifty-six patients and *Sh. sonnei* from eight patients.

Twenty-nine, or 45 per cent, of the patients from whom Shigella was isolated had convulsions. In the 100 from whom Shigella was not isolated, convulsions occurred in twelve patients, an incidence of 12 per cent.

The charts of these patients are reviewed with reference to temperature elevation, state of hydration, electrolyte disturbances, family and past history of convulsions, and spinal fluid findings in an attempt to find some explanation of the high incidence of convulsions in the patients with shigellosis. Reports of neurological manifestations in patients with shigellosis quoted in the literature are cited.

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THE PRODUCTION OF TEARS IN FAMILIAL DYSAUTONOMIA

Preliminary Report

Irving G. Kroop, M.D.
Brooklyn, N. Y.

THE clinical entity, familial dysautonomia, was first described in 1949 by Riley and associates.[1] The name of the disease implies a familial disorder of the autonomic nervous system. It is characterized by excessive perspiration, drooling, cold skin, erythematous skin blotches with excitement, emotional instability, hypertension, postural hypotension, and inadequate temperature control. In addition, poor motor coordination, absent or diminished deep tendon and corneal reflexes, and relative indifference to pain suggest a more diffuse involvement of the central nervous system. Defective lacrimation with absence of visible tears has been a characteristic, diagnostic, clinical feature of the disease. Corneal ulceration has resulted frequently in these patients because of deficient tearing and corneal hypalgesia.

An unexpected but apparently significant finding was obtained when acetyl β-methyl choline (Mecholyl) was injected subcutaneously as a test for pheochromocytoma in a patient with familial dysautonomia and paroxysmal hypertension. Mecholyl failed to stimulate a significant rise in blood pressure, but, surprisingly, caused the formation of visible tears. This chance observation prompted further study of the induction of lacrimation by Mecholyl in two other patients with familial dysautonomia.

All these patients showed absent corneal reflexes and diminished response to pinprick over the distribution of the trigeminal nerve. Irritation of the middle nasal turbinates by a twisting probe, and the odors of onions, concentrated ammonium hydroxide, acetic anhydride, and glacial acetic acid failed to produce tears. In addition, there was an obtunded reaction to these unpleasantly irritating odors. Unlike normal controls, the three patients with familial dysautonomia failed to sneeze and did not withdraw rapidly from these unpleasant stimuli.

In these same patients, ages 2, 6, and 14 years, Mecholyl, by subcutaneous injection in a dose of 3 mg. for the children and 5 mg. for the adolescent, produced drops of tears which rolled down the inner canthus. This dose of Mecholyl was the same as that required to produce tears in normal controls. Neostigmine methylsulfate (Prostigmin) 0.25 mg. subcutaneously was also effective.

These and other parasympathomimetic drugs may prove useful in the prevention and treatment of corneal ulceration in patients with familial dysautonomia. These observations also indicate that the lacrimal gland in

From the Department of Pediatrics, Jewish Chronic Disease Hospital.

familial dysautonomia can respond as a normal end organ, when stimulated directly by parasympathomimetic drugs like Mecholyl. The defect in lacrimation in this disease must therefore depend on an abnormality in the nerve pathways. The appreciation and effects of stimuli over the sensory afferent and central receptive pathways are distinctly defective in the three patients studied. It remains unknown whether there are additional defects in the central nuclei for psychic crying, and in the chemical transmission of impulses at the synapses of the parasympathetic efferent pathway.

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EXCHANGE TRANSFUSION IN PREMATURE INFANTS

EDGAR J. SCHOEN, M.D., AND ALEXANDER L. KING, M.D.
OAKLAND, CALIF.

THE successful performance of exchange transfusion in two very small infants (860 and 1,280 grams) with erythroblastosis fetalis appears to demonstrate the safety of this procedure. The smaller of the two infants died subsequently, but did not have kernicterus on post-mortem examination.

MATERIALS AND METHODS

Exchange transfusion was performed according to the technique described by Diamond and associates[12] with some modifications. A plastic catheter with a blunt tip was introduced directly into the umbilical vein, no metal cannula being used. Because of the size of the infants, 5 to 10 c.c. aliquots of blood were withdrawn and injected rather than the usual 20 c.c. aliquots. One cubic centimeter of 10 per cent calcium gluconate was injected through the catheter after the exchange of each 60 to 75 c.c. of blood rather than at 100 c.c. intervals. Readings of venous pressure were also made at 60 to 75 c.c. intervals, and a deficit sufficient to keep the venous pressure below 70 mm. water was maintained. Aliquots of blood were taken at the start, the midpoint, and the end of the procedure, and the serum bilirubin level of these specimens was determined by the Malloy-Evelyn method.[13]

From the Department of Pediatrics, Kaiser Foundation Hospital.

CASE REPORTS

CASE 1.—M. H., a 2 pound 13 ounce (1,280 grams) premature female infant, was transferred to the Kaiser Foundation Hospital on Jan. 18, 1955, via premature incubator at the age of 21 hours. The diagnosis was erythroblastosis fetalis. The mother was gravida vii, para ii. She had had a normal infant in 1944, followed by early abortions (all under three months) in 1946, 1947, 1950, and 1951. In 1949 she had given birth to a full-term infant who had erythroblastosis fetalis, but who survived following exchange transfusion and is now an apparently normal child. In 1952 she had delivered a full-term infant with hydrops fetalis who died thirty minutes after birth. In 1944, following the birth of her first child, she had had a transfusion reaction.

The genotypes of the family were as follows: mother cde/cde, father cDu e/CDe, sibling (aged 10 years) CDe/cde, sibling (aged 5 years) Cde/cde. On Jan. 14, 1955, four days before delivery of the infant, the maternal antibody titer (anti-C) was positive in 1:512 dilution.

The present gestation was uneventful and was estimated to be of seven months' duration. The premature infant was delivered with the aid of low forceps after a normal labor. The baby's color and cry were good at birth and she had an active Moro reflex. However, by the age of 3 hours she was icteric, and because the jaundice steadily increased she was transferred to this hospital at the age of 21 hours.

Physical examination on admission revealed an active female premature infant with a good cry and an active

Moro reflex. She was markedly jaundiced, but the liver and spleen were not palpable, and there was no edema. Laboratory studies shortly after admission revealed a positive Combs test, hemoglobin 16 Gm. per 100 c.c., red blood count 4.5 million, serum bilirubin 19 mg. per 100 c.c., and 18 nucleated erythrocytes per 100 leukocytes on blood spread. The infant's blood type was AB, Rh-positive (CDu e/cde).

At the age of 23 hours the infant was exchange transfused. With a No. 160 polyethylene catheter in the umbilical vein, 400 c.c. of type O, Rh-negative blood was injected in 10 c.c. aliquots, and 450 c.c. of blood was withdrawn (50 c.c. deficit). The room temperature was 70° F.; additional heat was supplied by padding the crib with hot-water bottles. Oxygen was administered during the procedure. After the exchange of each 75 c.c. of blood, the venous pressure was measured and 1 c.c. of 10 per cent calcium gluconate was injected into the polyethylene catheter. The initial venous pressure was 70 mm. water. The condition of the infant at the termination of the procedure was considered to be good, and she was returned to the incubator.

Penicillin, streptomycin, vitamin K, and ACTH were administered postoperatively. At the start of the exchange transfusion the serum bilirubin was 23 mg. per 100 c.c.; at the termination of the procedure it had fallen to 12.5 mg. per 100 c.c. Although the serum bilirubin level rose to 21 mg. per 100 c.c. twenty-four hours after exchange transfusion, within a few hours the level had spontaneously declined, making a second transfusion unnecessary. The postoperative course was otherwise uneventful. By age 5 days all medication was discontinued. At age 30 days the hemoglobin value was 7 Gm. per 100 c.c., and a small blood transfusion (30 c.c.) was given. Subsequently the infant did well, and was discharged from the hospital at age 58 days, weighing 5 pound 3 ounces. She was seen at two-week intervals in the outpatient department, no medication being prescribed. At the age of 5 months she weighed 10 pounds 5 ounces; her hemoglobin was 10.2 Gm. per 100 c.c. She could hold her head up well, arch her back when prone, shake a rattle, laugh out loud, and coo. There were no abnormal findings on neurological examination. She was thought to be a normal infant for her age, considering her prematurity.

Case 2.—D. C., a premature female infant, weighing 1 pound 14 ounces (860 grams) was born at Kaiser Foundation Hospital on Jan. 20, 1955, by frank breech delivery. Gestation was thought to have been twenty-six weeks. The membranes had ruptured prematurely. The cry was weak. The mother was gravida iii, para ii; her two previous children were apparently normal. Her blood was type A, Rh-negative; her husband's was type AB, Rh-positive. Her anti-Rh (anti-D) titer three weeks prior to delivery was positive in a dilution of 1:64.

When examined at the age of 2 hours the baby was slightly icteric; her cry was weak, the Moro reflex fair. There was no edema, hepatomegaly, or splenomegaly. Laboratory studies at age 2 hours yielded the following results: blood type AB, Rh-positive; Coombs' test positive; hemoglobin 11.2 Gm./ per 100 c.c.; red blood count 3.07 million; white blood count 71,700 with 63 per cent neutrophils and 37 per cent lymphocytes; there were 58 nucleated erythrocytes per 100 leukocytes. Serum bilirubin was 10 mg. per 100 c.c. at age 16 hours.

At age 24 hours exchange transfusion was performed, using the technique described in Case 1. Blood was exchanged in 5 c.c. aliquots. Two hundred fifty cubic centimeters was given and 265 c.c. removed (15 c.c. deficit). A total of 3 c.c. 10 per cent calcium gluconate was administered. At the termination of the procedure, which took 1 hour, 33 minutes, the infant appeared to be in satisfactory condition. Final venous pressure was 60 mm. water, pulse 128, and color fair. Postoperatively the infant was placed in an incubator and given penicillin, streptomycin, ACTH, and vitamin K at reg-

ular intervals. The serum bilirubin fell from a pre-exchange level of 12.9 mg. per 100 c.c. to a post-exchange level of 5.0 mg. per 100 c.c. At the age of 48 hours (twenty-four hours after exchange transfusion) the infant was still in fair condition. The serum bilirubin value was 7.5 mg. per 100 c.c. However, at age 60 hours the onset of respiratory distress was noted. The respirations became increasingly labored and finally were gasping in nature. At the age of 72 hours the infant died.

Pulmonary hemorrhage and atelectasis, believed to be the primary cause of death, were observed post mortem. The liver and spleen were congested, and gave evidence of a considerable degree of extramedullary hematopoiesis. The brain showed no sign of kernicterus.

DISCUSSION

Although we are unaware of exchange transfusion having been performed previously in infants of this size, the indications for the procedure seemed clear in these cases. Both mothers had elevated antibody titers. Both infants had erythroblastosis fetalis (positive Coombs' test), and both were immature.

In spite of their small size the infants tolerated exchange transfusion surprisingly well. During the procedure, a No. 160 polyethylene catheter was introduced into the umbilical vein with comparative ease, even in the infant weighing only 860 grams. Maintenance of body temperature would seem to be of prime importance during exchange transfusion in premature infants. In these cases hot-water bottles were used to aid in achieving this aim; if available, electric blankets and heated cribs may be used.

The smaller infant died about forty-eight hours after exchange. Although the pulmonary hemorrhage observed in this infant post mortem may have been related to erythroblastosis,[20] there was no evidence of kernicterus. The high mortality rate of infants whose birth weight is less than 1,000 grams is well known,[18, 19] respiratory tract abnormalities being the most common cause of death in this group.

The amount of blood exchanged in each infant was about 150 c.c. per pound of body weight. This amount would be considered excessive for full-term infants, in whom the calculated volume of blood for exchange transfusion is usually in the range of 70 c.c. per pound of body weight. However, it was felt that the larger volume was justifiable, on the basis of a greater lowering of serum bilirubin, as long as the infants were tolerating the procedure well, the venous pressure remained normal, and the time required to complete the exchange transfusion was not excessive (no longer than 1½ to 2 hours). In these cases the serum bilirubin was decreased to about 50 per cent of the pre-exchange levels. In addition, although blood volume is generally thought to be a function of body weight, Crawford and associates[15] cite evidence to show that blood volume is more a function of body surface area than of body weight. A 2 pound infant has only 25 per cent of the body weight of an 8 pound infant, but his body surface area (0.11 sq. m. vs. 0.23 sq. m.) is about 50 per cent that of the larger infant.

Theoretically there are at least two reasons why kernicterus is more common in premature than in full-term infants: (1) In premature infants, hyperbilirubinemia tends to occur "physiologically,"[9] and kernicterus has been shown to be related to hyperbilirubinemia.[1-4, 9-11] Exchange transfusion is recommended for any infant under the age of 5 days whose serum

bilirubin level is above 20 mg. per 100 c.c.[10, 11] (2) Kernicterus is more likely to develop in response to high serum bilirubin levels in immature animals than in mature animals.[1] Kernicterus has been described in premature infants who have had no evidence of erythroblastosis fetalis.[5, 8] Diamond and co-workers[10] have advised that exchange transfusion be performed in all infants with erythroblastosis fetalis whose gestation period is estimated to be less than thirty-eight weeks. Mollison and Walker[14] observed an increased mortality rate in erythroblastotic infants who had been delivered following early induction of labor, the increased mortality probably being due to an increased incidence of prematurity in the induced group.

SUMMARY AND CONCLUSIONS

The case histories of two small premature infants with erythroblastosis fetalis are presented. Both infants received exchange transfusion and both tolerated the procedure well. The smaller infant (860 grams) died about forty-eight hours after exchange transfusion, the primary cause of death being pulmonary hemorrhage and atelectasis. The larger infant (1,280 grams) survived with no apparent sequelae.

It is felt that these cases demonstrate the safety of exchange transfusion, even in extremely small premature infants. Thus, there would seem to be no reason for withholding exchange transfusion from a premature infant on the basis of size of the infant.

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CALCIFICATION AND OSSIFICATION OF THE ADRENALS IN A NINE-MONTH-OLD INFANT

OSCAR SCHWARTZ, M.D., AND HAROLD FINK, M.D.
BROOKLYN, N. Y.

BRUSCHWEILER[1] and Marine[2] have called attention to calcification in cats' adrenals and Kruse[3] has also noted ossification in a monkey's adrenal gland. Widman and associates[4] emphasized that dystrophic calcification occurs readily in dead or injured tissues. This has been observed in human adrenals with tuberculosis, neoplasms, Niemann-Pick disease or hemorrhage.

In children, the incidence of calcification in tuberculous adrenals is considerably lower than in adults.[5] Jaudin[6] included six such cases among his sixty-two patients under 15 years of age with tuberculous adrenals. Rolleston and Boyd[7] recorded a case in a 12-year-old boy.

Calcium deposits have been reported in a variety of adrenal neoplasms: Gellerstedt and Hjelm[8] in a ganglioneuroma, Wyatt and Farber[9] in six neuroblastomas, Samuel[10] in an adenocarcinoma, and Bartels and Cattell[11] in a pheochromocytoma. Willis[12] stated that groups of cells in neuroblastomas and ganglioneuromas may show calcification.

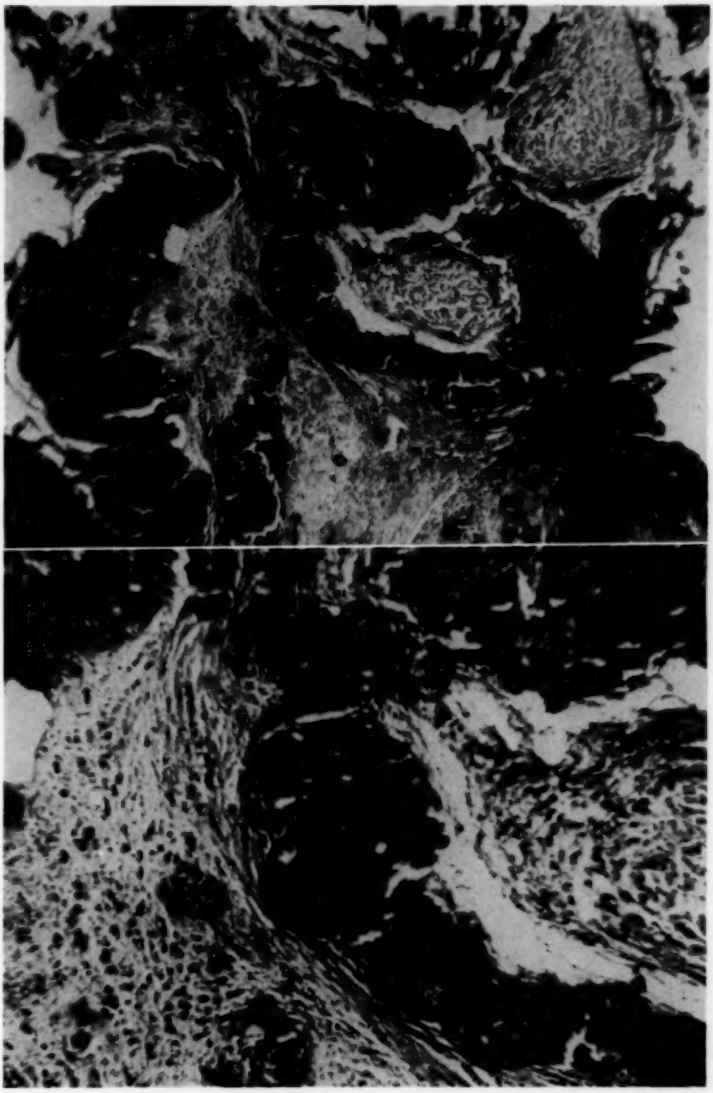
In the only reported case of Niemann-Pick disease[13] lipoid deposits were followed by calcification of the adrenals.

Hemorrhage has long been recognized as a major precursor of adrenal calcification.[14] Single case reports in children have been made by Newsam,[15] Stevens and Tomsykosky,[16] Rack and Eiben,[17] Lintz,[18] and Drucker and Rodriguez.[19] In the last case, increasing bilateral adrenal calcification was demonstrated by serial x-ray during life. In Rack's case, a chance abdominal x-ray revealed a calcified right adrenal associated with previous trauma. Early hemorrhage and calcification would explain the adrenal insufficiency noted between 2½ and 11 years in Lintz' case. Seligman[20] reported four adults with calcification in the adrenals which may have followed sublethal hemorrhages in the newborn period. Snelling and Erb[21] in a review of forty-three cases of adrenal hemorrhage among 3,637 autopsied children observed calcified adrenals in two newborn infants of 8 and 10 days and in six children aged 4 months to 5½ years. Two of these cases presented ossification with the presence of bone marrow. Kruse,[3] Newsam,[15] and Wooley[22] also reported ossification.

In the case reported here calcification and osseous metaplasia in the adrenals were unexpected findings at post mortem.

From the Department of Pediatrics, Dr. Sidney Nussbaum, Director, and the Department of Pathology, Coney Island Hospital. (Department of Hospitals, City of New York.)

A.



B.

Fig. 1.—*A*, Low magnification showing distribution of calcified areas in both cortex and medulla. (×30.) *B*, Higher magnification of calcified areas. (×100.)

CASE REPORT

A. T., No. 172451 C.I.H., a 9-month-old white female, was admitted Feb. 1, 1955, to the hospital with a history of severe difficulty in breathing, cough, vomiting, and slight fever of two days' duration. This was preceded by two weeks of a "running nose" without fever. The prior infant and neonatal history was uneventful. She was born at term by spontaneous vertex delivery and required no resuscitation. The birth weight was 3.9 kilograms. Family history was noncontributory.

On admission, she was a well-developed, well-nourished, cyanotic infant with labored asthmalike respiration. The pertinent physical findings were dullness and diminished breath sounds over the entire right chest and wheezing râles bilaterally. Mild nasal discharge, injected throat, and tachycardia were also noted.

Despite intensive therapy with antibiotics, digitalis, cortisone, oxygen, and blood transfusion, the cyanosis and dyspnea increased and a septic temperature with peaks of 106° F. appeared. Laboratory studies were not permissible by the patient's extremis condition. The patient died within twenty-four hours of admission. The post-mortem blood culture was negative.

Autopsy Findings.—A. T., female white infant (autopsy A55-018, Hosp. No. 172451) aged 9 months, weight 10.9 kilograms. The body was well developed. There were no gross bony deformities, jaundice, clubbing, eruptions, or palpable peripheral lymph nodes. The abdomen presented no palpable masses or viscera. The cavities had no significant amounts of fluid. No adhesions were present.

The lungs were uniformly expanded but rubbery in consistency. The pleurae were smooth. The trachea and main bronchial divisions were filled with tenacious mucus. All lobes were heavy and sunk in water. The cut surfaces were granular, leaving a frothy sanguinous fluid on the knife edge. The bronchi were prominent, with surrounding beefy granular

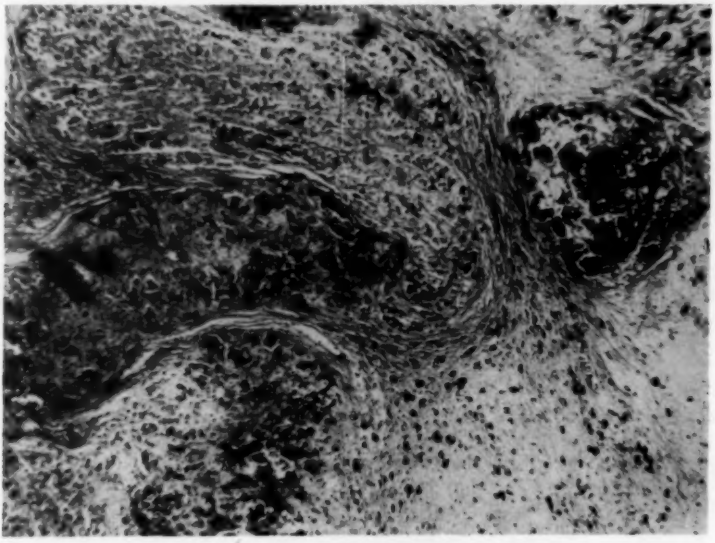
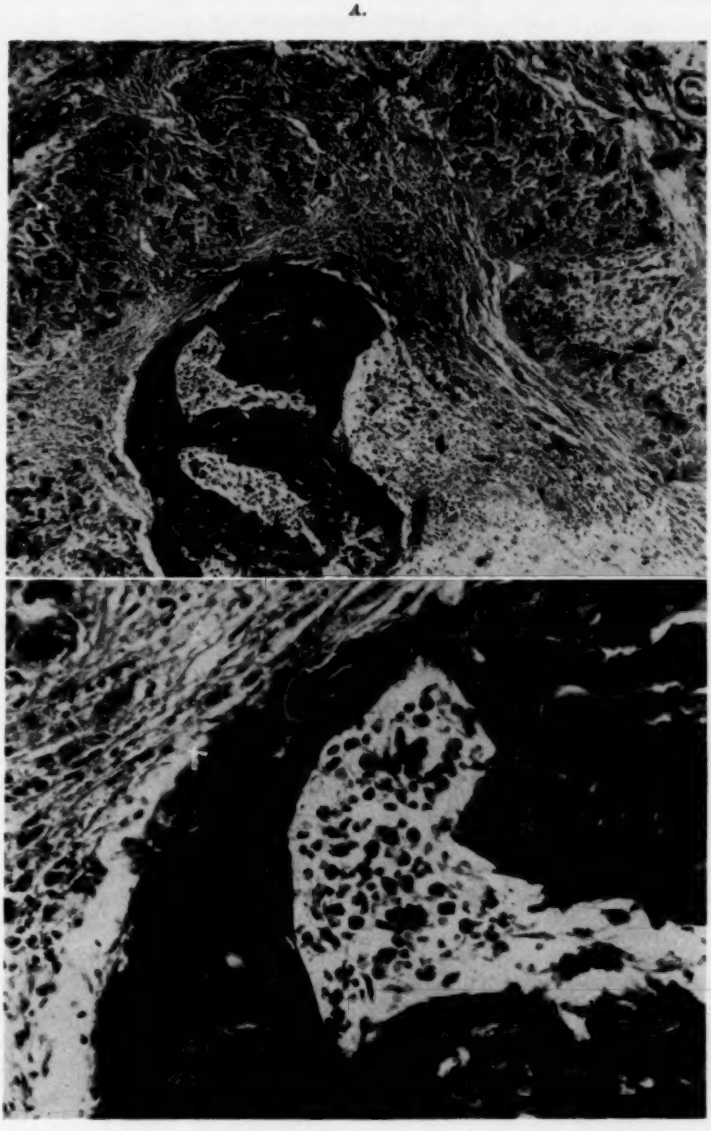


Fig. 2.—Area of adrenal cortex, showing acute degenerative changes in all layers. (×100.)



A.

B.

Fig. 3.—*A*, Ossified area in medulla. (×100.) *B*, Ossification with central marrow. (×400.)

areas. There were several enlarged hilar nodes. The largest of these measured 2 by 0.8 by 0.3 cm. The nodes were soft, red-brown, with moist, firm, cut surfaces.

On microscopic examination the bronchioli were filled with cells of various types, vacuolated macrophages, erythrocytes, polymorphonuclear leukocytes, and scattered monocytes. The peribronchial tissue was edematous, with engorged vessels. The stroma showed numerous compact areas of polymorphonuclear leukocytes and lymphocytes. Throughout, the alveoli contained acute inflammatory exudate with intervening scattered groups of intact, well-aerated alveoli.

The heart, liver, kidneys, spleen, parotid gland, thyroid gland were all within normal limits. There were scattered enlarged mesenteric nodes which were soft and nonconfluent. On section, each showed a moist, tan cut surface. Histologic sections showed nonspecific changes.

Each adrenal was prominently located in the usual site. Each weighed 4 grams and measured 3 by 2 by 1 cm. They maintained their cocked-hat shape and were bright yellow to brown. On palpation each was stony hard. On section both cortex and medulla were rigid and brittle. The outline of cortex was maintained as a brighter yellow than the somewhat yellow-gray medulla. Lime salt deposition was present throughout both regions except for minute soft areas. Histologic preparations showed a similar deposition of calcium. There were isolated areas of recognizable cortical cells. These cells were swollen, with a finely vacuolated cytoplasm. Throughout both cortex and medulla there were groups of hemosiderin-laden macrophages. These showed a positive reaction with Perle's stain.

In each adrenal were areas of ossification. Between the bony spicules were either loose fibrillar fibroareolar tissue or cellular areas composed of myeloid and erythroblastic cells with an occasional multinucleated cell suggesting a megakaryocyte.

The pathologic features of degeneration, calcification, ossification, and bone marrow formation in the adrenals are shown in Figs. 1, *A* and *B*, 2, 3, *A* and *B*.

DISCUSSION

The nature of the respiratory infection and the clinical significance of the adrenal calcification warrant further comment.

The patient's prolonged expiratory dyspnea with wheezing was a manifestation of acute generalized obstructive emphysema caused by bronchiolitis, peribronchiolitis, and interstitial pneumonitis. The dyspnea is not to be confused with that seen in allergic asthma, an extremely rare condition at 9 months of age. The pathogenesis of interstitial pneumonitis is initially a destruction of bronchial mucosae by viral, mechanical, or congenital factors. The latter two agents are not applicable here as there was no history of, or evidence of, foreign body aspiration or mucoviscidosis. Following the initial damage, a secondary bacterial invasion of the interstitial tissues and extension into the interalveolar septums and alveoli occur. The physical findings may be altered, as in our case, by superimposed consolidation or plugged bronchi. Interstitial pneumonitis is probably the most frequent type of pneumonic death in infants under 1 year of age and may readily be the sole fatal agent in our case.

The post-mortem findings of bilateral adrenal calcification invites speculation of the contributory role of acute adrenal insufficiency in the death of the patient. Calcification was probably secondary to adrenal hemorrhage in the newborn period. Approximately sixteen similar cases have been recorded.[16] Neonatal adrenal hemor-

rhage is usually caused by trauma to the relatively large, vascular glands in the course of difficult delivery, breech delivery, or in resuscitation of the newborn infant. No significant perinatal history was obtained in our case. Another possible etiological factor, hemorrhagic disease of the newborn, as cited by Snelling and Erb[21] in one case, was not applicable here. The negative blood culture would tend to eliminate sepsis as a factor. In the newborn infant, sepsis does not play the essential role it does in older children, where meningococcemia is responsible for 60 per cent[23] and other bacteremias[24] for the remaining adrenal hemorrhages.

Although over 150 cases of neonatal hemorrhage were known, Geppert and co-authors[25] emphasized that very few had been recognized and studied ante mortem. In their clinical experience they have found 1 in 10,000 newborn infants with symptoms of adrenal hemorrhage. In post-mortem studies, Snelling and Erb[21] report an incidence of adrenal hemorrhage of 1.19 per cent.

Clinically neonatal adrenal hemorrhage is characterized by manifestation of acute adrenal insufficiency, often superimposed by features of internal hemorrhage. Initial attention may be focused by the acute elevation of temperature, rapid respiration, cyanosis and negative lung findings, labeled "pseudopneumonia of the newborn" by Goldzieher and Gordon.[26] Petechiae, purpuras, hypoglycemia, vomiting, diarrhea, dehydration, uremia, irritability, coma, and convulsions may be present. Signs of internal hemorrhage may be evident by shock, vascular collapse, weak pulse, subnormal temperature, abdominal distention, and palpable renal masses. The latter are present when hemorrhage dissects into the retroperitoneal spaces.

Very few patients have survived severe hemorrhagic destruction of the adrenals. Sezary[27] has claimed that life is possible when as much as 90 per cent of the adrenals are destroyed. The residual functioning glandular tissue, following sublethal neonatal hemorrhage, may carry the child asymptomatically through adulthood and be recognized only at post mortem.[20] Another possibility following such early hemorrhage is latent adrenal insufficiency with manifestations appearing later in infancy or childhood.[18] Finally there are clinical cases ending in sudden deaths[15, 16, 19, 21] during the stress of severe infection. In these cases the adrenal reserves are inadequate to produce and sustain the necessary adaptation responses of Seyle.[28]

It is conceivable that failure of adaptation played a definite role in our case. One is justified in this thought whenever nonspecific stress places sudden demands on previously impaired adrenals. Two cases illustrating this were reported by one of us (H. F.).[20]

When such cases are recognized, it is mandatory to use in therapy adrenal steroids, saline, glucose, and water. A strong index of suspicion should exist whenever a significant perinatal history is obtained. Roentgenographic evidence of calcified adrenals is most helpful if found, but does not exclude previous hemorrhages when absent. We were not fortunate enough to be alerted by a related history or positive x-rays. However, the possibility of acute adrenal insufficiency was considered in the presence of a rapidly fulminating illness, and the above therapeutic measures were used. Unfortunately the

patient died before any therapeutic response could occur.

SUMMARY

1. A case report of a 9-month-old child with fulminating interstitial pneumonitis and with calcification and ossification of the adrenals has been presented.

2. The adrenal changes were secondary to hemorrhage which occurred probably at birth.

3. It is believed that acute adrenal insufficiency may have played a significant role in the rapid exitus of the patient.

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CAPILLARIA HEPATICA

Report of Fourth Case of True Human Infestation

George M. Ewing, M.D., and I. L. Tilden, M.D.
Honolulu, Hawaii

Capillaria hepatica is a nematode discovered by Bancroft in 1893 which belongs to the order Enoplida, superfamily Trichuroidea, and family Trichuridae.[1] It is a cosmopolitan parasite of rodents and has also been found in rabbits, dogs, pigs, monkeys, and other animals. It rarely produces disease in the human being, only three cases having been reported up to the present time.

HUMAN INFESTATION

Spurious cases have been reported by McQuown[2, 3] and others in which the ova of this parasite have been found in the stool. The finding is usually transient and not associated with symptoms; the ova are noninfective, apparently heat killed, and are merely "passing through" the gastrointestinal tract. In McQuown's two cases they originated from the ingestion of wild squirrel liver used to prepare dressing and gravy.

The first genuine case of human infection by *Capillaria hepatica* was reported by McArthur[2, 4] in 1924. The patient was a 20-year-old British soldier who died after three years of service in India. The liver at autopsy showed areas of suppuration containing a large number of *Capillaria hepatica* ova microscopically.

From the Departments of Pediatrics and Pathology, Straub Clinic.

The second case was reported by McQuown[2] in 1950. The patient was a 17-month-old Negro child who entered Charity Hospital in New Orleans acutely ill with an enlarged liver and symptoms of pneumonitis. Death occurred twenty-six hours after admission, and at necropsy the liver was enlarged and presented 1 to 3 mm. grayish tan areas resembling focal areas of necrosis. Microscopically, granulomas were present in the periportal spaces filled with ova of *Capillaria hepatica*. No adult parasites were demonstrated but one area was present containing hyalin debris and foreign body giant cells which appeared to be the site of removal of a dead parasite.

The third case was a 7-year-old Negro female with sickle-cell disease reported by Otto and associates[4] in 1954. The child's illness was characterized by nosebleed, fever, anorexia, lethargy, malaise, hematemesis, hepatosplenomegaly, anemia, and eosinophilia. Early in the illness, an adult ascarid was passed and ascarid eggs were found in the feces. On treatment with hexylresorcinol, two more ascarids were passed after which the stools became negative.

The eosinophilia persisted and the liver continued to enlarge. On the forty-sixth day of hospitalization a

liver biopsy was done at laparotomy which showed complete disruption of architecture by a parasitic infection with necrotic foci containing adult worms and ova of *Capillaria hepatica*. A second biopsy was done on the one hundred eighty-sixth hospital day which showed pronounced scarring, many intact ova often within giant cells, but no evidence of maturation of larvae and no remaining adult worms. The ova from a teased portion of liver developed in tap water.

Nearly two years after the onset of the acute illness thought to mark the parasitic infestation, the patient entered the hospital with weakness, nosebleed, anorexia, a protuberant abdomen, anemia, and eosinophilia. Death occurred two months later with respiratory arrest.

At necropsy the liver, heart, spleen, and kidneys were greatly enlarged. The liver showed increased scarring and many eggs were still present, some undergoing dissolution and some within giant cells. Caseous foci containing shadowy remnants of dead adult worms were seen. A solitary tuberculoid focus was present in the lungs containing hyalin and calcific bodies, and the renal glomeruli were large and cellular. A few foci of calcification were present within renal tubules.

CASE REPORT

M. L., a 15-month-old female Caucasian infant, was first seen by Dr. Walter C. Griggs, of the Lapahoehoe Sugar Plantation on the Island of Hawaii, on Nov. 9, 1954. Her illness began two weeks previously with fever, anorexia, cough, constipation, and reluctance to walk. The family had a sick kitten and also kept dogs. According to the parents, the child had been known to eat dirt.

A stool specimen examined by Dr. Griggs contained large numbers of ova resembling those of Ascaris (?). The initial white blood count was 30,700 with 9 per cent neutrophils, 33 per cent lymphocytes, 2 per cent monocytes, and 56 per cent eosinophils. Two courses of hexylresorcinol were given, following which urticaria and edema of the eyelids developed, subsiding after oral Benadryl. The child was hospitalized because of fever (which failed to respond to Terramycin) and pulmonary congestion.

One week later the white count had dropped to 13,600 with 27 per cent neutrophils, 54 per cent lymphocytes, and 19 per cent eosinophils. Two urine examinations were negative and two subsequent stool examinations were negative for ova and parasites. A course of Atabrine was given on Nov. 23, 1954.

On November 22 the white count was 18,200 with 26 per cent neutrophils, 53 per cent lymphocytes, and 18 per cent eosinophils. Moderate anemia was present, the red cell count being 3,600,000 and the hemoglobin 9 grams. The spleen was palpable and the liver was enlarged to 3 or 4 fingerbreadths below the right costal margin.

The child was sent to the pediatric department of the Straub Clinic in Honolulu on Nov. 25, 1954. Initial examination showed a chronically ill, pale, 15-month-old female infant with a prominent abdomen. She weighed 20½ pounds and was 29½ inches tall. The liver was enlarged to 5 fingerbreadths below the right costal margin, smooth with a sharp edge and slightly tender, and the spleen was enlarged 1 to 2 fingerbreadths below the left costal margin. The abdominal veins were prominent, the skin turgor poor, and the skeletal musculature flabby.

A chest x-ray showed increased prominence of the linear markings compatible with bronchitis. A tuberculin test (PPD No. 1) was negative. The red blood count was 3,280,000 and the hemoglobin was 9.4 grams. The white blood count was 14,550 with 35 per cent neutrophils, 33 per cent lym-

phocytes, and 30 per cent eosinophils. The Kunkel flocculation test was elevated to 26 units (normal 3 to 12) and the thymol turbidity test to 26 units (normal 0 to 5). The total protein was 7.2 grams with reversal of the A/G ratio (globulin 4.2, albumin 3.0), the sedimentation rate (Wintrobe) greatly elevated—34 mm. in one hour—and the heterophil agglutination test positive in a 1:800 dilution but negative when the serum was absorbed with guinea pig kidney and beef cell antigen.

James Cherry* performed a biopsy of the liver through a right rectus incision. The liver was greatly enlarged and the surface was studded with pearly white granulomatous lesions varying in size from pin point up to 1 to 2 mm.

Pathologic Examination.—Microscopic examination of the liver biopsy showed massive deposition of ova within the portal areas together with many parasites (Fig. 1). There was an associated severe inflammatory reaction with considerable destruction

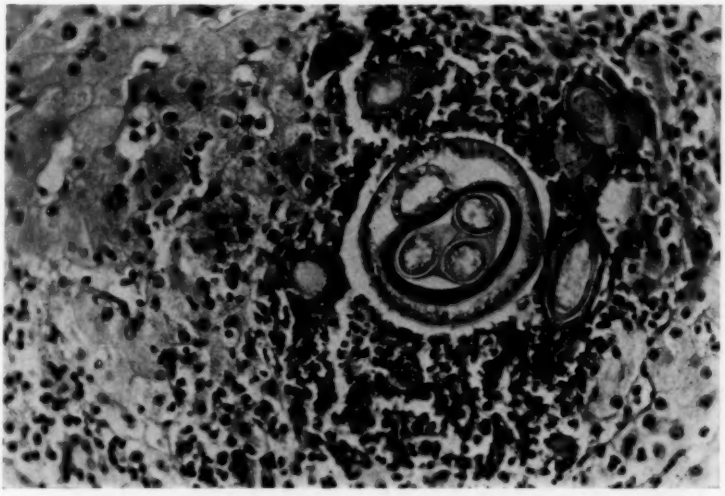

Fig. 1.—Adult parasite containing ova with four surrounding eggs in portal area of liver. (H & E; ×265.)

The patient was given a ten-day course of Hetrazan,* 2 c.c. three times a day, and started on Lederplex,† 4 c.c. twice a day. She had a poor appetite and fever persisted to as high as 101° F. daily. She was given 200 c.c. of whole blood in preparation for liver biopsy. She was admitted to Kauikeolani Children's Hospital, in Honolulu, and on Dec. 3, 1954, Dr.

of liver tissue toward the periphery of the lobules. The inflammatory process was manifested by diffuse infiltration of lymphocytes, plasma cells, eosinophils, and histiocytes. There was an occasional giant cell but there were no epithelioid cell tubercles or circumscribed granuloma with necrotic centers such as described by others. Toward the center of the liver lobule, the liver cells were well preserved and appeared relatively normal.

The ova were oval in shape and were approximately 60 microns long

*Hetrazan, an organic compound effective in treatment of ascariasis and filariasis, a brand of diethylcarbamazine.

†Lederplex, a brand of vitamin B complex containing vitamin B_1, B_2 niacinamide, pyridoxine, B_6, pantothenic acid, choline, folic acid, inositol, soluble liver fraction, and B_{12}.

*Department of Surgery, Straub Clinic.

and 30 to 35 microns wide. They had a double shell with a pitted or radiating effect between the two shells (Fig. 2) and a bilateral protuberance at each end although the ends were smooth externally. At first *Trichuris trichiura* was suspected; more careful study revealed the ova to be those of *Capillaria hepatica*. A slide and the case history were sent to Dr. Albert McQuown[5] who concurred in the diagnosis.

Subsequent Course. — The patient was discharged from the hospital on the day of surgery and seen frequently thereafter in the office. She was given a low fat, high protein, and high calorie diet and continued on Lederplex, one teaspoonful twice daily. Although the patient was clinically improved after surgery with less fever and better appetite, the liver and spleen showed no apparent decrease in size. The red blood count and hemoglobin were still moderately depressed two weeks after surgery and the white blood count was high, 27,200, with neutrophils 33 per cent, lymphocytes 19 per cent, and eosinophils 46 per cent. A repeat stool examination was negative for ova, cysts, and parasites.

The patient was sent back to her home in Lapahoehoe, Hawaii, to continue on the same diet and medication with Lederplex indefinitely. Her older sibling, a girl 2 years 9 months of age, was checked for ova in her stools on two occasions and none were found. Interestingly enough, her white blood count was 6,700 with 15 per cent eosinophils, although there was no enlargement of the liver or spleen and no symptoms.

The child did quite well for about four weeks after returning home, having a better appetite and a return of muscular strength. A cold then developed which was associated with weight loss, fever, cough, and loss of appetite, and she developed pneumonia. She was brought to Honolulu on Feb. 9, 1955, and admitted to the Kauikeolani Children's Hospital in critical condition. She had physical signs of diffuse bronchopneumonia, the liver was enlarged 6 fingerbreadths below the right costal margin, and the spleen 3 fingerbreadths. Her extremities were wasted, and she had persistent cough and dyspnea.

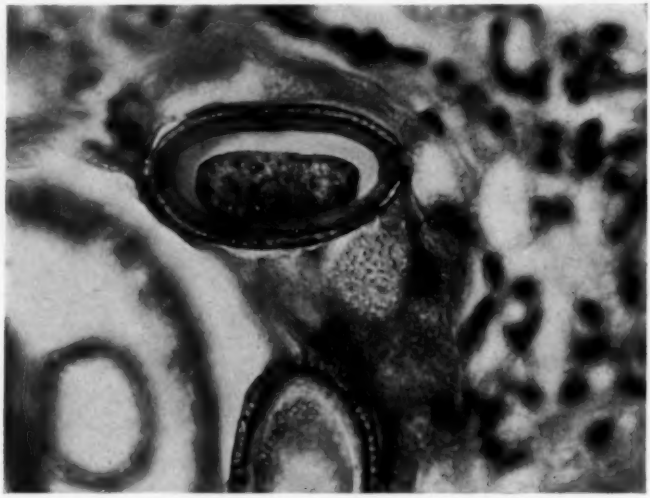

Fig. 2.—Photomicrograph to show detail of ovum. Note oval-shaped, bilateral protuberance at each end but a smooth outer shell, and the double wall with radiations or striations between the two shells. (H & E; ×840.)

Treatment consisted of continuous oxygen, penicillin and streptomycin, blood transfusion, intravenous and subcutaneous fluids, and parenteral vitamins, but she went downhill and died on Feb. 16, 1955, a week following admission and a little less than four months after the onset of her illness. She received ACTH the last forty-eight hours of life without apparent benefit. Laboratory work showed leukocytosis of 18,250 with 23 per cent eosinophils on admission which decreased to 8,750 on the fourth day with 80 per cent neutrophils and 4 per cent eosinophils. This leukopenia was thought to represent a response to a viral infection of the intestine manifested by fever, diarrhea, and anorexia. On the day of death, the count was 32,900 with 79 per cent neutrophils and 21 per cent lymphocytes with no eosinophils. The thymol turbidity test was elevated to 10 units, the Kunkel to 42 units, and the serum albumin was 2.5 grams per cent, the globulin 3.9 grams per cent.

A post-mortem examination was performed by Dr. Thomas Fujiwara on Feb. 17, 1955. All lobes of both lungs were consolidated, presenting a red granular cut surface, and the tracheobronchial tree contained mucopurulent material. The spleen was enlarged, weighing 98 grams, and presented the appearance of septic hyperplasia. The liver was greatly enlarged, weighing 840 grams, and showing a salmon-pink cut surface mottled with irregular yellowish gray streaks and patches.

Microscopically, the liver showed innumerable ova chiefly in the portal areas which could still be identified as those of *Capillaria hepatica* although many showed evidence of dissolution and degeneration. The parasites themselves, however, were degenerated and were represented by hyalinized granular deposits surrounded by palisaded histiocytes and giant cells or by calcified fragments associated with foreign body giant cells (Fig. 3). The liver cell destruction, especially toward the periphery of the lobule, was pronounced, and the resulting fibrosis had produced considerable distortion of the normal architecture. The centrally located liver cells, however, were normal morphologically; there was little evidence of liver cell regeneration.

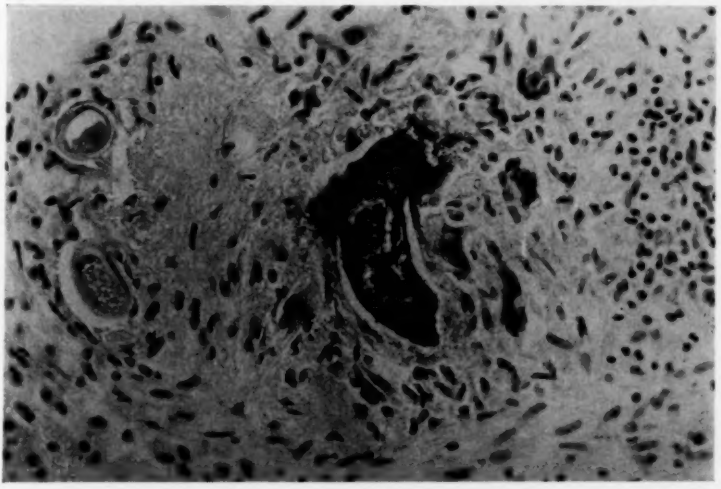

Fig. 3.—Photomicrograph (autopsy) showing two fairly well-preserved ova at the left in portal area of liver and calcified parasite in center. (H & E; ×265.)

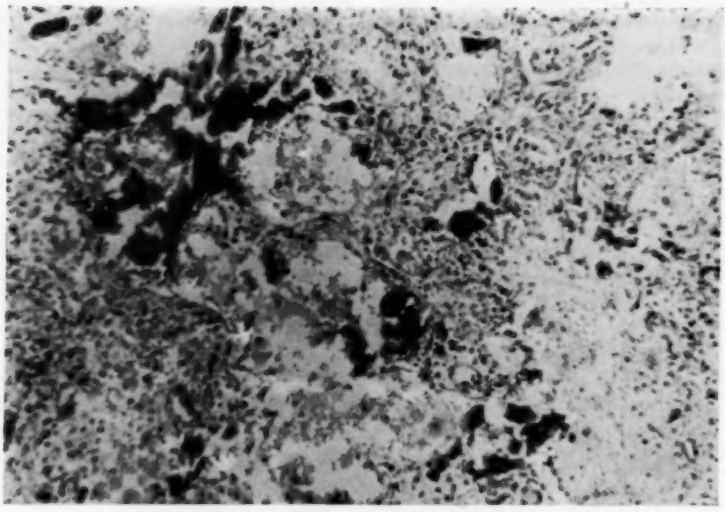

Fig. 4.—Calcified fragments in lungs probably representing fragments of degenerated and calcified parasites. (H & E; ×130.)

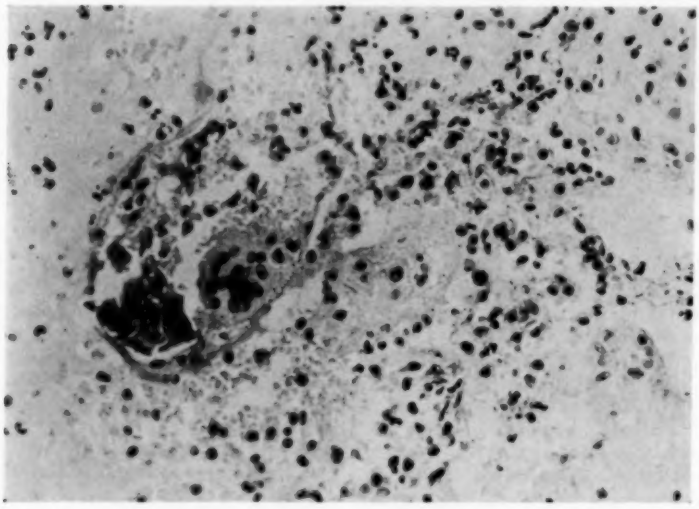

Fig. 5.—Photomicrograph of lung section showing foreign body giant cell adjacent to calcific fragment. (H & E; ×265.)

The microscopic picture in the lungs was of even greater interest and was remarkably uniform in the sections taken from all parts of both lungs. Fluid, red cells and histiocytes, some containing hemosiderin, were present within the alveolar spaces and the alveolar walls were thickened. There were only a few scattered neutrophils so that nowhere was the usual picture of pneumonic consolidation observed. The most outstanding finding was the presence of many irregular fragments of calcified material within the alveolar walls and spaces and these were often associated with foreign body giant cells (Figs. 4 and 5). This provides at least presumptive evidence of parasitism of the lungs probably by larval forms of *Capillaria hepatica* perhaps at the time of the original infestation.

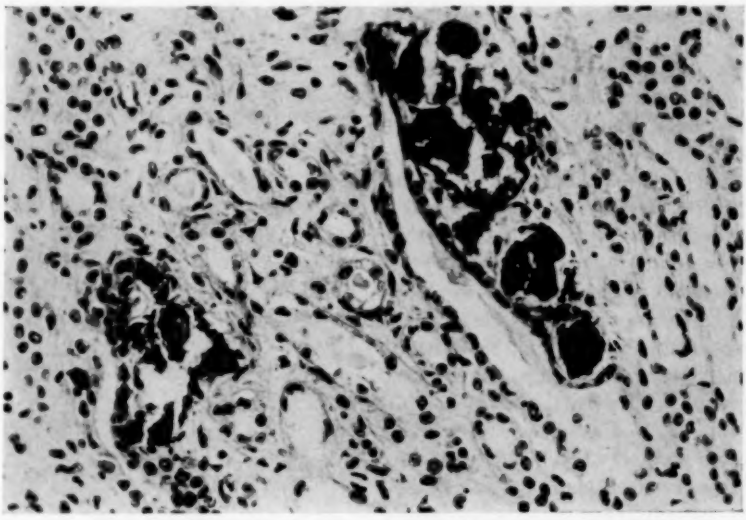

Fig. 6.—Calcific fragments between renal tubules. (H & E; ×265.)

The kidneys also contained many irregular calcified masses *between* tubules and glomeruli, some of which were recognizable as being *within* vessels, suggesting that they had reached the kidneys by embolization through the blood stream (Fig. 6).

DISCUSSION

The life cycle of *Capillaria hepatica* is still not completely understood. It is thought that the infection is acquired by ingesting embryonated eggs which hatch in the intestine and reach the liver through the portal blood stream where the worms mature in three to four weeks. The eggs are released in the liver upon the disintegration of the adult worms and remain there undeveloped until the death of the host. Under natural conditions this may occur as a result of cannibalism of rats. The ova are liberated in the gastrointestinal tract and pass out in the feces. They become embryonated and infective in four to six weeks in a suitable external environment.

In the patient described by Otto and associates[4] and in our case also, the diagnosis was established before death

by liver biopsy. At first the diagnosis was thought to be visceral larva migrans due to the dog ascaris (*Toxocara canis*) since the signs and symptoms were indistinguishable from reported cases of this disease. Actually, liver biopsy is the only means of definitive diagnosis is a child with hepatosplenomegaly, eosinophilia, and constitutional symptoms. So far as this particular parasite is concerned, a needle biopsy would probably suffice, since in the three reported cases and our case also the hepatic involvement was widespread and massive.

This nematode is an extremely common parasite of rats. Luttermoser[6] found them in the livers of 86 per cent of more than 2,500 adult rats examined post mortem in Baltimore, and 7 of 12 rats trapped on the Island of Hawaii (where the child acquired the infection) showed the ova of *Capillaria hepatica* in the liver. In these positive rat livers, there is very little tissue reaction around the eggs which are always located in the portal areas. It is not surprising therefore that a dirt-eating child living on rat-infested premises should develop the disease. Indeed, it is surprising that more children of this sort are not infected, and it seems possible that the disease may exist in a nonfatal, perhaps subclinical, form in children with unexplained eosinophilia. The ova of this parasite do not appear in the feces, except fleetingly, and diagnosis would be possible only by liver biopsy.

The necropsy findings in the case herein reported are indicative of an overwhelming infection with probable involvement of the lungs as well as the liver. In this respect the case is similar to the one reported by Otto and coauthors[4] except that they found only one lung granuloma and in our case there were many calcified fragments in both lungs surrounded by foreign body giant cells. Calcification between renal tubules was a conspicuous feature and in some instances the calcific material was located within vessels, suggesting the possibility of embolization of the kidneys by calcific fragments from the lungs.

SUMMARY

A fatal case of *Capillaria hepatica* infestation is described in a 15-month-old Caucasian child with death occurring a little less than four months after the onset of the illness. The diagnosis was made before death by means of liver biopsy which showed many parasites and their ova within the liver. This is the fourth instance of genuine human infestation to be reported and the second instance in which the diagnosis was made during life. The clinical symptoms and laboratory findings were similar to those seen in children with visceral larva migrans due to *Toxocara canis*, the dog roundworm. The presence of calcific fragments and foreign body giant cells in the lungs suggests pulmonary involvement by the parasites or their ova, and similar calcific fragments in the kidneys may have reached that location through the blood stream.

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LISTERIA MENINGITIS

PETER L. MATHIEU, JR., M.D., RAYMOND M. YOUNG, PH.D., ERNEST P. MENNILLO, M.D., AND EDWARD S. SHERWOOD, M.D.
PROVIDENCE, R. I.

THE organism causing listeria meningitis was first isolated from rabbits by Murray and associates in 1926,[8] and was described under the name of *Bacterium monocytogenes* because of the mononuclear leukocytosis which occurred in these animals. The generic name Listerella was created by Pirie[9] for an identical organism obtained from an epizootic in wild rodents, but since this proved to be a homonym, he subsequently proposed the generic term Listeria and named the organism *Listeria monocytogenes.*

The first report of human listeria infection in this country is that of Burn[3] who isolated the organism from each of four fatal cases; three were from newborn infants, and the fourth from an adult. Kaplan[6] reviewed twenty-three cases of listeria meningitis appearing in the literature prior to 1945. Since that time approximately a dozen cases have been reported. Girard and Murray[4] made an extensive survey of the role of *L. monocytogenes* as the cause of disease in man and animals. Before the use of sulfonamides and antibiotic drugs, human listeria infection was usually fatal. Handelman and co-workers[5] reported a patient with listeria meningitis who responded to penicillin and sulfadiazine. Other reported cures with one or both of these drugs followed. Broad spectrum antibiotics have been reported used successfully by Binder and associates[2] who used streptomycin and chloramphenicol, and Portero and Despirito[10] who used Aureomycin and chloramphenicol.

The recent literature on human listerellosis would indicate that the infection is quite rare; however, the infection is probably more common than realized. Murray[7] points out that some 150 cases are described in the German literature besides a number of cases reported in this country and Canada and a number of cases not published. The reason that more cases have not been diagnosed very likely has been due to two sources of confusion with regard to identifying the etiological agent. Since *L. monocytogenes* morphologically resembles the common corynebacteria and also possesses other characteristics of the diphtheroids, it no doubt has been overlooked and considered a contaminant or nonpathogen. Reports in the literature, early as well as recent, would indicate this to be the case; in fact some of the recent reports have indicated that the organism was first reported a diphtheroid and then more careful study showed it to be *L. monocytogenes.* Another source of confusion is that *L. monocytogenes* appears as a small, round colony with clear

From the Department of Pediatrics and the Laboratory, Rhode Island Hospital.

zone hemolysis on blood agar quite like colonies of beta streptococci, and the organism has a tendency to form short chains in trypticase-soy broth so that it has been mistakenly assumed to be a beta streptococcus. The recent literature shows at least one report of where the organism was first called a beta streptococcus and subsequently identified as *L. monocytogenes.*

The purpose of this paper is to report two cases of listeria meningitis with recovery from the acute infection following antibiotic therapy and to point out distinctive characters of *L. monocytogenes* which differentiate this organism from diphtheroids and other gram-positive rod bacteria it might be thought to resemble.

CASE REPORTS

CASE 1.—P. McB. This was the first Rhode Island Hospital admission of this 7-week-old Negro male who was admitted Jan. 3, 1950, with a chief complaint of irritability and fever of twenty-four hours' duration.

He had been delivered by cesarean section at seven months, weight 4 pounds 1 ounce. He had been discharged apparently well on the fifth day and continued so until four days before admission, when constipation with hard bowel movements developed. Reportedly he had vomited several times in the four days before admission. On the afternoon before admission, the patient became irritable, whined frequently, and cried on light touch. It was noted that the remainder of the family had coryza. The physician noted a temperature of 102° F. and the baby was hospitalized. He had been given a formula of evaporated milk.

Three siblings and the parents were well, except for coryza. There was no history of tuberculosis, syphilis, diabetes, or allergy, also no known exposure to any contagion.

The baby was a dehydrated, poorly nourished infant weighing 6 pounds 8 ounces, with feeble cry, irritability, spasticity and quivering. The baby was staring and popeyed. The pupils were myotic. There was congestion of the nasal mucous membranes, and the pharynx was filled with mucus. The anterior and posterior fontanels were patent. There was separation of all suture lines and the anterior fontanel was bulging and doughy with crackpot sound to percussion. There was marked nuchal rigidity. The heart and lungs were unremarkable. The pulse rate was 160 to 200 per minute, with a regular rhythm, and respirations 28. The abdomen was tense. All four extremities were somewhat spastic and were noted to have coarse tremors. Deep tendon reflexes were 2 plus to 3 plus. The Brudzinski sign was positive. Kernig's signs were not available.

Laboratory Findings.—The white cell count revealed 14,650 cells per cubic millimeter, of which 72 per cent were polymorphonuclear leukocytes, 25 per cent lymphocytes, 2 per cent metamyelocytes, and 1 per cent myelocytes. The spinal fluid contained 7,200 white cells per cubic millimeter, of which 99 per cent were polymorphonuclear leukocytes. The total protein was 304 mg. per cent, the glucose 15 mg. per cent, and the chloride value 595 mg. per cent. The spinal fluid was cloudy and turbid with slightly increased pressure. The gram-stained smear showed positive rods. Culture showed a gram-positive aerobic rod which was identified as *Listeria monocytogenes.* The Listeria species was sent to the communicable disease center of the U.S. Public Health Service at Chamblee, Georgia, where identification was confirmed by serotyping.

Hospital Course.—The patient entered the hospital with a temperature of 102.5° F., acutely ill, weighing 6 pounds 8 ounces. The temperature ran a spiking course for three days and then reverted to normal on the fourth hospital day and remained so until discharged. Treatment consisted of

penicillin, streptomycin, chlortetracycline, and sulfadiazine by mouth. On the third hospital day the patient received 100 c.c. of whole blood. He also received several clyses to maintain fluid balance. He received several spinal fluid examinations after the initial tap and these were all negative. On the eighth hospital day streptomycin was omitted; on the eleventh hospital day sulfadiazine was omitted; chlortetracycline was omitted on the twelfth day and penicillin was omitted on the sixteenth day.

By the third hospital day the fontanels were normal in consistency. By the fourth day his irritability had cleared and he was discharged on his twenty-first hospital day, having gained 6 ounces and being completely asymptomatic.

CASE 2.—G. R., a 3-week-old male infant was admitted Jan. 22, 1955, because of "cold and blue feet." The infant had been born at a local obstetrical hospital and was reported to be a full-term normal delivery with normal prenatal course. Immediate neonatal course had been normal; the baby being discharged from the obstetrical hospital on breast feedings, which were continued for two weeks and then changed to evaporated milk. Two days prior to admission the baby developed a cold consisting of a "stopped-up" nose and "running" eyes. The baby became anorexic and he vomited once. The parents noted that the baby's feet became cold and turned blue approximately three hours prior to admission, and for this he was brought to the hospital.

The family history was noncontributory.

Review of the systems was negative, except for constipation of two days' duration.

Physical examination revealed a thin, slightly dehydrated white male infant in considerable distress. The baby was cyanotic and had a pulse which at the time of the first examination was well above 200 per minute. Several minutes later it was found to be 120, returning to over 200 shortly thereafter. Fontanels were open but not bulging. There was a slight nasal discharge. The chest was clear. Examination of the heart was negative except for the tachycardia. The liver was palpated 3 cm. below the right costal margin. Fingernails and toenails were cyanotic. Femoral pulses were normal.

Laboratory Data.—The white cell count revealed 38,600 cells, of which 58 per cent were polymorphonuclear leukocytes, 32 per cent lymphocytes, 5 per cent monocytes, and 5 per cent band cells. Blood serum sodium was found to be 135 meq. per liter, potassium 6.1 meq. per liter, chloride 87 meq. per liter, and carbon dioxide 32 meq. per liter. The chest x-ray revealed a small area of infiltration in the right lower lobe consistent with pneumonitis. X-ray three days later showed complete clearing. The spinal fluid showed 9,000 white blood cells per cubic millimeter, which were nearly all polymorphonuclear leukocytes, and a total protein of 728 mg. per cent. Culture of this fluid grew out a pure culture of an aerobic gram-positive rod which was identified as *Listeria monocytogenes.* The organism was sensitive to penicillin, streptomycin, chloramphenicol, chlortetracycline, oxytetracycline, tetracycline, and erythromycin.

An electrocardiogram was done at the time of admission and showed a tachycardia of 143 and a P-R interval of 0.16, which was considered somewhat prolonged for a patient of this age at this rate.

Hospital Course.—While in the accident room, the baby on two occasions stopped breathing, the first occasion being relieved with artificial respiration, the second requiring intubation and aspiration. The immediate impression was that the baby had a paroxysmal auricular tachycardia; however, the possibility of meningitis was considered and lumbar puncture performed. Within a few hours it was noted that the fontanel was rapidly becoming tense and full, and the baby's

temperature, which had been normal on admission, became somewhat elevated.

The baby was digitalized at the time of admission and as soon as the diagnosis of meningitis was ascertained, he was started on intravenous fluids, and was given antibiotic drugs including penicillin intramuscularly (200,000 units stat, 100,000 units every four hours), streptomycin intramuscularly (100 mg. stat, 75 mg. every eight hours), Gantrisin intravenously (0.3 Gm. stat, 0.2 Gm. every eight hours), and tetracycline intravenously (50 mg. stat, 50 mg. every twelve hours). The electrolytes gradually returned to normal under fluid and electrolyte therapy, and the baby's condition gradually seemed to improve.

A subdural tap was done on the third hospital day and found to be negative. Repeated attempts were made to re-enter the lumbar subarachnoid space, but these attempts were unsuccessful until the seventh hospital day at which time 9 c.c. of xanthochromic, cloudy fluid was removed. The cell count of this fluid showed 281 red blood cells per cubic millimeter, 19 polymorphonuclear leukocytes, and 18 lymphocytes. The total protein was 652 mg. per cent, and the glucose was 26 mg. per cent.

Another lumbar puncture was performed on the twelfth hospital day and total protein on that occasion was found to be 680 mg. per cent. Subsequent subdural taps were negative, and the lumbar puncture on the twentieth hospital day revealed 7 polymorphonuclear leukocytes, 39 lymphocytes, a glucose of 46 mg. per cent and total protein of 286 mg. per cent. Spinal fluid cultures after the original one showing *Listeria monocytogenes* were negative.

The head circumference at the time of discharge was 35.7 cm. The baby was discharged on the twenty-second hospital day with no apparent neurological or bacteriological residue.

Second Admission.—Four days after discharge, the baby was readmitted because of a "cold" and because the mother felt that the baby could not see. The fontanel was found to be bulging and tense. A lumbar puncture revealed 675 red blood cells and 675 lymphocytes per cubic millimeter. The glucose content was 35 mg. per cent and the protein, 180 mg. per cent. Culture for bacteria showed no organisms. The head size at the time of admission was 39.4 cm., and four days later the head circumference was 40.7 cm.

Neurosurgeons were consulted and by means of simultaneous ventricular and lumbar tap and dye injections determined the presence of a noncommunicating hydrocephalus. Ventricular air studies revealed a large ventricular system without communication to the subarachnoid space. On the nineteenth day of the second admission a posterior fossa exploration was performed revealing a fourth ventricle block with inflammation and exudate. A right Torkildsen ventriculocisternostomy was performed. At the time of operation the head circumference measured 43 cm. Subsequent head measurements went up to 45.5 cm., and the neurosurgeons performed a ventriculoperitoneal shunt which has required several revisions.

BACTERIOLOGY

Isolates from both cases conform to the characteristics ascribed to *Listeria monocytogenes* as outlined in *Bergey's Manual of Determinative Bacteriology.*[1]

Morphology.—The organism was seen readily in the gram-stained smear of sedimented spinal fluid in both of the cases. It appeared as a small gram-positive rod about 0.5 by 1 to 2 microns in size, but larger rods also were seen, and some showed a tendency to curve and were comma shaped, especially after artificial cultivation. There was no evidence of branching; the organism did not form spores and was not acid-fast. Some authors be-

lieve that *L. monocytogenes* should be placed in the genus *Erysipelothrix;* however, *L. monocytogenes* is a motile species, an important distinctive trait, while other gram-positive rod bacteria with which it might be confused are nonmotile. These include the following genera: Erysipelothrix, Nocardia, Lactobacillus, and Corynebacterium (diphtheroids). Motility is best demonstrated after incubating the culture at room temperature for twelve to eighteen hours and is rather sluggish. Only a few cells in a microscopic field show motion, and this may be described as a tumbling end-over-end movement.

Cultural Traits.—*L. monocytogenes* is not a fastidious organism with regard to cultural and nutritional requirements; it will grow readily on the usual routine culture media after incubation overnight. The colonies are small and round, measuring about 1 to 2 mm. in diameter, and resemble beta streptococci since they form a definite zone of beta hemolysis about them which is especially marked after forty-eight hours.

Biochemical Traits.—This organism ferments glucose, sucrose, and salicin with acid formation but no gas. Maltose and lactose show slow acid formation, but there is no action on mannitol. Growth in a broth containing 6.5 per cent sodium chloride and growth at 4° C. aid in differentiating this organism from other gram-positive rod bacteria with which it might be confused.

Sensitivity to Antibiotic Drugs.—The organism isolated from Case 1 was tested for sensitivity to penicillin and was found to be sensitive; it was inhibited by less than 0.007 unit penicillin per cubic centimeter.

The organism isolated from Case 2 was found to be sensitive to seven antibiotic drugs including chloramphenicol, chlortetracycline, oxytetracycline, tetracycline, erythromycin, penicillin, and streptomycin.

COMMENT

Infections with *L. monocytogenes* have been described throughout the world in both human beings and domestic animals. Murray[7] notes that listerellosis has been reported from twenty-six countries in four continents, ranging from the Arctic to the tropics The organism has been isolated and identified from twenty-seven animal species, and it appears to be primarily an animal pathogen. In domestic animals it may produce a severe fatal disease such as meningoencephalitis in cattle, sheep, and goats, or the organism may be isolated from animals with little or no indication of illness, in which case a carrier state probably exists. Little is known about the transmission and maintenance of this organism. Since a number of the reported cases of human infection have been in infants but a few days old, it would seem that the infection may occur by way of the placental or vaginal route. The organism has been isolated from the genital tract of several animal species.[4]

The two isolates from the above cases were inhibited by small amounts of antibacterial drugs, and these findings were supported by therapeutic response in the two patients. It should be emphasized that therapy must be continued until two spinal fluid tests are entirely normal and the patient is clinically well. Portero and Despirito[10] report that insufficient therapy with chlortetracycline and chloramphenicol,

at least, may cause the organism to develop resistance to these drugs. In 1945, before sulfonamide drugs were used in the treatment of listerellosis, the mortality rate was 74 per cent in the reported cases. Now with broad spectrum antibiotic drugs, the patients in the few cases reported have responded well, with the organism showing sensitivity to all agents.

Our experience with the second patient, who was adequately treated with antibiotic drugs yet developed exudate and noncommunicating hydrocephalus, raises the question of incidence of this complication. In future cases one might consider the use of enzymes intrathecally to lyse these exudates and one should be vigilant in detecting a block early in the treatment.

A striking observation in Listeria meningitis in both of our cases and also in those reported in the literature has been the misleading symptomatology. The newborn infant may have poor feeding, diarrhea, cyanosis, drowsiness, or convulsions. Our second case was felt to be a cardiorespiratory case with recurrent apnea until it was suggested that the infant might have a meningitis.

Listeria meningitis simulates tuberculous meningitis in several respects. The spinal fluid may be clear. In both cases the spinal fluid shows a pleocytosis with polymorphonuclear leukocytes predominating early and then lymphocytes predominating later in the course of the infection. One must consider listerellosis in a case such as this, for if the organism can be isolated and identified, the prognosis may be altered greatly and the prolonged therapy indicated for tuberculous meningitis will be unnecessary.

Listeria infections in human beings are no doubt much more common than the literature would indicate. It is very likely that *L. monocytogenes* isolated from patients with meningitis has been called a diphtheroid because of similarity in cell and colony morphology, or a beta streptococcus because of similarity in colony appearance on blood agar. This organism is not at all fastidious in regard to cultural and nutritional requirements as is true of the more common bacterial etiological agents of meningitis. However, if this species is kept in mind when examining spinal fluid, and if the isolate is observed carefully for distinctive identifying traits, more cases of Listeria infection will be diagnosed.

SUMMARY

Two cases of meningitis caused by *Listeria monocytogenes* are reported with case histories and mode of therapy. Both recovered from the acute infection after treatment with multiple antibiotics.

A striking observation in this infection is the misleading symptomatology, which may not suggest a meningitis. Moreover, the meningitis when recognized many simulate tuberculous meningitis in several respects so that isolation and identification of the etiological agent is imperative.

Distinctive characters of *L. monocytogenes* are described which differentiate the organism from diphtheroids and other gram-positive bacteria it might be thought to resemble.

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A SURVEY OF POLICIES AND PRACTICES FOR HOSPITALIZATION OF CHILDREN IN NORTHERN CALIFORNIA

Luigi Luzzatti, M.D.
San Francisco, Calif.

IN THE past few years several articles have appeared in scientific journals[1-5] and in the lay press on problems related to the hospitalization of children. In order to evaluate what actually takes place in hospitals caring for children it was thought important to know the actual policies and practices carried on in several hospitals, together with the pediatrician's thinking on the matter.

About a year ago the Mental Health Society of Northern California became interested in the subject of the hospitalization of children in preparation for a discussion on this topic at the International Mental Health Congress held in Toronto in 1954. A committee, representing several disciplines concerned with the care of children in hospitals, was set up in the Bay area. This committee was composed of five pediatricians, one instructor of pediatric nursing, one director of occupational therapy in a children's hospital, one social case worker, and one nursery school teacher who had been connected with a children's hospital. Statistical advice was obtained through the School of Public Health, University of California in Berkeley. The Northern California Pediatric Society and the Northern California Section of the American Academy of Pediatrics gave their support to the committee and its activities and selected one pediatrician to represent them on the committee.

Questionnaires were sent to the administrators of all 183 hospitals in Northern California according to a list supplied by the California State Department of Public Health. One hundred eleven questionnaires were returned; of these twelve were not included in this report because the hospitals were either not in operation at the time or admitted no children, leaving a total of ninety-nine hospitals that could be used for this study.

Two hundred forty-one questionnaires were sent to all the members of the Northern California Pediatric Society. One hundred twenty-eight were returned, or 51.6 per cent of the total. Eleven of the members were nonpracticing pediatricians. One hundred twenty-four questionnaires could be used for the study obtained from 53.9 per cent of the practicing pediatricians in Northern California (230).

The breakdown of the hospitals reporting is outlined in Table I. The non-short term special hospitals are too few and were not considered in this report. There was no significant difference, so far as the size of the hos-

From the Departments of Pediatrics and Preventive Medicine, Stanford University School of Medicine.

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pital is concerned, in percentage of those who answered or did not answer the questionnaire. A nurse (director of nursing or pediatric supervisor) participated in answering about one-half of the questionnaires for the governmental hospitals, either alone or with other staff members; the hospital administrator answered only half as often as the nurse. Physicians answered only about one-eighth of the questionnaires. For nonprofit and proprietary hospitals, nurses and administrators answered equally, with only a few physicians participating.

This preliminary report will not deal with a detailed analysis of the questionnaire but only with some general considerations obtained from the study.

Table I. Number of Hospitals Reporting

METROPOLITAN		%	RURAL	%	TOTAL	%
Governmental	10	90.9	21	58.3	31	66.0
Nonprofit	23	74.2	16	50.0	39	61.9
Proprietary	6	50.0	18	50.0	24	50.0
Non-short term					5	38.5
Total	39	72.2	55	52.9	99	57.9

ORIENTATION PRIOR TO ADMISSION

In general all hospitals reported that an attempt is made to orient the children prior to the hospitalization. The answers were not revealing; most of them dealt with general statements like "Yes, they are told what to expect" or "The routines are explained," etc. One hospital stated "We welcome visits before admission so that the child may see his bed and meet his nurses," and another one "welcomes visits to show the instruments to the child." The nurse plays a prominent role in such an orientation; in those hospitals where the answer to the orientation was a positive one and a responsible person was mentioned, the nurse was responsible alone or with other personnel in about 80 per cent of the hospitals. This figure is even higher in Government hospitals. The physician is responsible for the orientation of the patient prior to admission in only a few hospitals and more in nonprofit and proprietary hospitals than Government hospitals. From the answers to the questionnaires, it appears that social workers play only a secondary role in this capacity and practically only in nonprofit hospitals; Government hospitals which have the largest number of social service departments scarcely utilize social workers in this role. Only one out of twenty-six proprietary hospitals has a social service department.

Only thirteen out of seventy-six hospitals have printed material available for parents or children before admission to the hospital and of these thirteen, twelve are nonprofit hospitals. Most of these provide information related to policy or financial matters only. Only four of the twelve nonprofit hospitals have printed material on matters other than policy and finances. Actually only one small pamphlet dealing with matters other than financial or of policy was sent to the committee by the hospitals answering the questionnaire.

In this respect it is interesting to note that approximately one-third of the practicing pediatricians utilize literature available to orient parents and children to the hospitalization, and that many of them asked for information concerning such literature or wished that some were available.

POLICIES FOR HOSPITALIZATION

In about 76 per cent of all hospitals reporting, the mother is allowed to accompany the child to the room or ward, to assist in putting the child to bed, and to remain beyond that period. In 9.5 per cent there were one or more "no" answers to these three questions. There was no significant difference so far as the hospital census, the size of the hospital, the geographical location, or the type of hospital were concerned. About 72 per cent of all hospitals reporting question the parents on admission on the child's habits, words used for elimination, nickname, etc.; but only eight per cent of these keep a record of this information that can be utilized by those caring for the child. About 90 per cent of all hospitals allow or encourage the children to bring in their toys or personal objects; this includes all of the nonprofit hospitals, and about 77 per cent of the Government hospitals. Smaller census hospitals as a whole allow such procedures less often than large census hospitals.

One-third of all hospitals did not answer a question related to continuity of nursing care and an additional 15 per cent of all hospitals did not seem to understand the question. In the other half of all the hospitals there seems to be an attempt made to provide continuity of nursing care within the eight-hour shift.

The orientation of the patient to hospital routines such as temperature taking, staying in bed, masks, etc., and to special procedures such as anesthesia, laboratory tests, surgical procedures, etc., is again chiefly the responsibility of the nurse, who performs such function in about 82 per cent of the hospitals that answered this question positively and mentioned a responsible person. Physicians (private or resident staff) were the next responsible person in about 34 per cent of the hospitals. All the hospitals that answered these questions said that they do make an attempt to explain procedures to children beforehand, like "What it is, what to expect and whether or not it will hurt." In some hospitals the anesthetists meet the children before surgery and plan for story-telling before the anesthesia. It seems evident from the answers that larger hospitals with larger children census and metropolitan hospitals have more of a planned procedure for this orientation than small hospitals in rural areas, who do not seem to have a definite plan, but depend largely on the interest of the individual involved, the amount of time available, etc.

Only about 18 per cent of the hospitals that answered have an occupational therapy department with a range from 26.6 per cent for government hospitals to 5.9 per cent for proprietary hospitals. Thirty-four per cent of the hospitals answering the question have volunteers and these are overwhelmingly in large-sized, big census hospitals; none of the proprietary hospitals has a volunteer service, and only 5.4 per cent of the rural hospitals do. Playroom facilities are available in 19.5 per cent of the hospitals answering and again a great majority are in large hospitals, 42.0 per cent in urban, and only 4.3 per cent in rural hospitals. None of the proprietary hospitals has playroom facilities.

VISITING HOURS

In Table II the answers to the question relating to visiting hours are tabulated by census and size of hospital and by geographical areas. The first group "none to 2 hours a day" includes those hospitals where visiting is not allowed at any time (only one

large-sized Governmental hospital, where it was indicated that the rules will be changed in the near future) or those hospitals where daily visiting is not allowed. The word "flexible" relates to those hospitals where there are no fixed rules for visiting by the parents but where the visiting privileges are left to the discretion of either the physician or the parents.

In Table III the visiting hours are tabulated by type of hospital and geographical location. It appears that nonprofit and proprietary hospitals have less restricted visiting hours than Government hospitals, especially so in the rural areas, where none of the nonprofit or proprietary hospitals reported half of the hospitals reporting have rather liberal visiting hours.

TABLE II. VISITING HOURS BY CENSUS AND SIZE OF HOSPITAL

	NONE TO 2 HR. A DAY	ABOVE 2 HR. TO FLEXIBLE	UNKNOWN	TOTAL NO. OF HOSPITALS
Daily Census				
Under 15	16.4*	58.2	25.4	67
15 and above	57.2	33.3	9.5	21
Unknown	—	—	—	6
Hospital Beds				
Under 100	5.3	64.9	29.8	57
100 and above	56.7*	29.8	13.5	37
Metropolitan areas	43.6	35.9	20.5	39
Rural areas	12.8*	61.8	25.4	55
Total	25.6	51.0	23.4	94

*One Governmental hospital allows no visitors at any time.

TABLE III. VISITING HOURS BY TYPE OF HOSPITAL AND GEOGRAPHICAL LOCATION

	NONE TO 2 HR. A DAY	2 HR. TO FLEXIBLE	UNKNOWN	TOTAL NO. OF HOSPITALS
Governmental	45.2	38.7	16.1	31
Nonprofit	23.1	56.4	20.5	39
Proprietary	4.2	58.3	37.5	24
Total	25.6	51.0	23.4	94
Metropolitan area				
Governmental	70.0	20.0	10.0	10
Nonprofit	39.1	39.1	21.8	23
Proprietary	16.7	50.0	33.3	6
Total	43.6	35.9	20.5	39
Rural areas				
Governmental	33.3	47.6	19.1	21
Nonprofit	0	81.2	18.8	16
Proprietary	0	61.1	38.9	18
Total	12.8	61.8	25.4	55

Though there are several hospitals for which the visiting rules are not known, there seems to be a tendency for the smaller hospitals to be more liberal and for the larger hospitals to be more strict so far as visiting is concerned. Also rural hospitals seem to permit more visiting than hospitals in metropolitan communities. In general, about visiting hours in the "none to 2 hours a day" group.

It is interesting to look at these tables in the light of the answers obtained from the pediatrician's questionnaire (Table IV). Over one-fourth of the practicing pediatricians who answered the questionnaire would put no limitations upon visiting by parents

in the hospital and less than one-fourth would definitely restrict it, while the other half would limit it or individualize it according to the reaction of the parents or the child to the visiting. In this group many pediatricians felt that the child's crying at the separation should not be an indication for decreasing visiting time but rather for increasing it.

COMMENTS

From the onset the committee recognized the limitations imposed by an evaluation of the problem under study obtained through questionnaires. One of these limitations is undoubtedly a bias resulting from the fact that only people interested in this problem would be likely to answer. It was also realized that some answers might possibly be directed to conform with accepted opinions on the subject rather than reflect entirely the established practices in a particular hospital. An attempt was made to obviate these factors by phrasing the questions in a way that could lead to an expression of different or opposite opinions. A suggestion was made in an accompanying letter to the hospital administrators that the chief of pediatrics and the directors of nursing, social service, and the occupational therapy departments be consulted before filling in the questionnaire. As mentioned previously, this suggestion was followed only in a few hospitals.

In any case it was felt that the questionnaire in itself would be likely to stimulate interest and possibly discussion around this topic. This proved to be correct, as revealed in some of the answers and as it became known later that some hospitals had made the questionnaire a subject for discussion on this particular problem.

The interest aroused in the community by this study can also be demonstrated by the fact that members of the committee participated in several panel discussions or presentations, radio broadcasts, and television shows on the hospitalization of children under the sponsorship of lay groups or educational institutions within a few months after the formation of the committee.

As a whole, one can say that hospitals in Northern California are well aware of the problems connected with the hospitalization of children. It seems that the small hospitals in the outlying rural communities, proprietary or otherwise, have less facilities conducive to proper adjustment of the child to hospitalization, lack of facilities for occupational therapy, volunteer help, and playrooms, they seem to have a less planned attempt to orient the child to what goes on in the hospital, and to make hospital personnel

TABLE IV. PEDIATRICIAN'S QUESTIONNAIRE—VISITING HOURS

	NO.		PER CENT	
Not limited	36		27.5	
Limited	73		55.7	
None to 2 hr. day		27*		20.6
Above 2 hr. to flexible		10		7.6
Limited but unspecified		29		22.2
Meal or bedtime only		7		5.3
Individualized	17		13.0	
Unknown	5		3.8	
Total	131†		100.0	

*One M.D. would not allow parents in the hospital.
†Some questionnaires had multiple answers.

aware of the child's needs. On the other hand, visiting hours are more flexible and liberal; parents are brought in with greater ease. One can certainly postulate that with smaller staffs and fewer children the chance for a good relationship between patient, parent, and professional personnel is an excellent one and that this obviates the handicaps that small hospitals may have in making available to the children the most modern techniques of hospital care.

It is interesting to note the secondary role that social workers play in the orientation of children and parents prior to hospitalization. This has always been considered one of the classical functions of a social service department in a hospital.

Though the answers to the pediatrician's questionnaire were not dealt with extensively in this report, it seemed evident that the pediatrician's thoughts on these matters as a whole reflect an awareness of the needs of parents and children and a changing philosophy in the problems of child care in the hospitals.

SUMMARY

Policies and practices for hospitalization of children in Northern California were studied by means of questionnaires sent to all hospitals and all practicing pediatricians in that area. A general evaluation of the answers showed that most hospitals and pediatricians are well aware of the problems related to children in hospitals. Small hospitals in rural areas make up for the lack of facilities conducive to proper adjustment of the child to hospitalization by having more flexible and liberal visiting rules.

Members of the "Committee on the Hospitalized Child" were:

Mrs. Elizabeth Elkus, formerly Head Nursery School Teacher, Child Development Center, Children's Hospital of the East Bay, Oakland.

Dr. David Friedman, formerly Department of Pediatrics, Kaiser Foundation Hospital, Oakland.

Dr. Samuel Hurwitz, Pediatrician, San Francisco.

Mrs. Barbara Judkins, School of Social Welfare, University of California, Berkeley.

Mrs. Bella Rhoades, formerly Director of the Department of Occupational Therapy, Children's Hospital, San Francisco.

Dr. George Shade, Department of Pediatrics, University of California Medical School.

Miss Kathryn Smith, Assistant Professor of Pediatric Nursing, University of California School of Nursing, San Francisco.

Dr. H. E. Thelander, Chief of the Department of Pediatrics, Children's Hospital, San Francisco.

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Clinical Pathological Conference

CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

A 12-week-old female infant was admitted to the hospital because of vomiting and diarrhea for a period of five weeks.

The patient was one of fraternal twins, born in turn to a 28-year-old primigravida. The pregnancy was uneventful and the mother's diet was said to be adequate. The delivery was easy, and the patient's condition was good. The birth weight was recorded as 4 pounds 12 ounces. The infant was placed on a commercially prepared formula on which she did well until 5 weeks of age, when she developed "sniffles," which lasted only a few days, and then began to regurgitate the formula. On being changed to whole milk, Karo, and water formula she again did well until the age of 7 weeks. Cod-liver oil preparations and 2 ounces of orange juice were given from 1 month of age. At 7 weeks of age she weighed 6 pounds 12 ounces. She then began to vomit about one-half of each of her feedings and developed diarrhea, with three or four loose, watery green stools a day; these did not contain blood. Her appetite continued to be good and her oral intake amounted to 32 ounces daily. At 9 weeks of age the vomiting increased and became projectile in character. The stools increased to five or six a day. Her weight dropped to 5 pounds 10 ounces. At 12 weeks of age she was placed on a sugar-water formula, which was taken well without vomiting or excess stools, but because of her general condition admission to the hospital was advised.

The mother and the father are well. The twin sibling has done very well, weighing 7¾ pounds at 3 months of age, beginning from a birth weight of 5 pounds.

Physical examination, on admission, revealed a temperature of 98° F., a pulse of 120 per minute, and a respiratory rate of 40 per minute. The weight was 5 pounds 10 ounces. The circumference of the head was 33 cm. and the length was 51 cm. The patient was small and pale, with evidence of marked wasting and almost no subcutaneous fat. The infant, however, was alert and in no discomfort. The tongue appeared smooth, the inguinal nodes were readily felt, and there was a small, easily reduced right inguinal hernia. There was no evidence of active infection, and the remainder of the physical examination was negative.

Laboratory examination: Three examinations of the urine revealed no abnormalities. The hemoglobin of the blood was 7.9 Gm. per cent, the erythrocyte count 1.6 million per cubic millimeter. The hematocrit was 24 per cent, the white blood count 9,200 per cubic millimeter, with a differential of polymorphonuclear cells 32 per cent, lymphocytes 67 per cent, and monocytes 1 per cent. There was 1 megaloblast and 1 normoblast per 200 leukocytes in the peripheral blood smear. The reticulocytes numbered 2 per cent, platelets 640,000 per cubic millimeter. Examination of the blood film revealed a moderate poikilocytosis and anisocytosis, with a tendency toward macrocytosis of the erythrocytes. The serum nonprotein nitrogen was 15.5 mg. per cent, with a protein of 5.7 Gm. per cent. The Hinton test was negative. Examination of the stool revealed a semisolid, greenish material, culture of which grew out *Bacillus proteus*. Cultures of the nose and throat grew a moderate number of *Staphylococcus aureus* and many *Colobactrum coli*. A fasting sample of the gastric fluid revealed 4 units of free hydrochloric acid, with a total acidity of 8 units. The aspiration of the bone marrow was said to be consistent with megaloblastic anemia. A roentgenogram of the abdomen on admission showed numerous fluid levels in the small intestine, but no distention. The peritoneal lines were preserved. A roentgenogram of the chest was normal. A film of the metacarpals and phalanges showed a slight coarseness of the trabecular pattern.

The infant was initially given intravenous fluids and nothing by mouth, with prompt cessation of her diarrhea. Thereafter, she was given oral electrolyte solution, and two days after admission was started on folic acid by mouth, 100 mg. daily. These medications were continued throughout admission, but were later given parenterally. Clinically, the diarrhea improved on clear fluid, but with each attempt to offer skimmed milk the diarrhea recurred. There was no vomiting, the infant's temperature ranged from 97° to 98° F., falling to hypothermic levels with each exacerbation of the diarrhea. The infant's general appearance, vigor, and appetite remained unchanged until two days before death. Penicillin, 15,000 units every three hours, was started six days before death, although no definite infection was found; this was continued until demise.

After institution of folic acid and vitamin C therapy, the hemoglobin ranged from 7.8 to 9.5 Gm. two days before death. The reticulocyte count reached a high of 6.4 per cent and then fell to 4.2 per cent. The peripheral leukocyte count was 21,800, with a marked shift to the left; but then fell to 11,000 per cubic millimeter terminally. The peripheral platelet count ranged from 512,000 to 390,000 per cubic millimeter and fell terminally on the day of death to 76,000 per cubic millimeter. Two days before death the patient was clinically dehydrated and had lost 6 ounces in weight; she seemed more irritable. Accordingly, intravenous therapy was again started, with a transfusion of 65 c.c. of blood, which was followed by other fluids.

The day before death the patient passed a large "current-jelly" stool with clots. Examination revealed the

abdomen to be minimally distended but soft, and no masses were felt. The rectal examination was negative, but was followed by the passage of another large collection of clotted blood. The infant was given 150 c.c. of blood, a surgical consultation was obtained, and an exploratory laparotomy was performed. At the time of operation, the small bowel contained many punctate areas of hemorrhage but no Meckel's diverticulum, no intussusception, ulcer, or polyp was found. She was returned to the ward in fair condition.

For the first ten hours, postoperatively, the patient seemed to do very well, with good color, and appeared alert. At this time the respirations were noted to be stertorous, and the baby became less responsive and died in respiratory failure, thirteen hours postoperatively. Just before death she passed another large bloody stool. During the last thirty-eight hours of life, intravenous fluids were given as follows: They totaled 1,255 c.c., and included 215 c.c. of whole blood, 90 c.c. of plasma, 255 c.c. of normal saline, and 695 c.c. of dextrose and water. On the day of death the blood hemoglobin level was 15 Gm. per cent and the erythrocyte count was 3.96 per cubic millimeter.

DISCUSSION

DR. LEONARD APT.—* The formula that was given was a proprietary one, made up to simulate the relative proportions of breast milk in regard to protein, carbohydrate, and fat; its protein content is about 1.7 per cent, carbohydrate 6.7, fat 3.3 per cent. One of the comments that may be made in regard to this formula before we pass on is that in 1947 the company still did not include ascorbic acid in the formula. We will see a little later on why vitamin C, in regard to this type of formula, is important in so far as the type of anemia is concerned. A cod-liver oil preparation was given and 2 ounces of orange juice, starting at the age of 1 month. I think that this would be optimal in regard to therapy in a patient who is considered premature. As we know, a premature infant, because of rapid growth and the decreased stores of vitamin C, requires much more than the normal full-term newborn infant. The amount of ascorbic acid in 2 ounces of orange juice is approximately 30 mg., and I believe also that this is below the optimal amount that should be given to a premature infant. It has been emphasized again by Dr. S. Z. Levine's group in New York in dealing with the metabolism of premature infants that there is an incomplete oxidation of the aromatic amino acids, phenylalanine and tyrosine, and with lack of vitamin C there is actual loss of the intermediate metabolites. He found that approximately 50 and preferably 100 mg. of ascorbic acid is the amount that should be given to premature infants in the first or second week of life.

Given a baby at this age, with the story of vomiting and diarrhea, there are many possibilities in regard to diagnosis, and because of the subsequent stories I think it would be well to think over in general what the symptoms of vomiting, diarrhea, and prematurity may have to do with the gastrointestinal tract. The possibilities are infection, gastrointestinal anomaly, incomplete absorption due to some

*Dr. Apt is a former Assistant Physician, Children's Medical Center.

enzyme difficulty, metabolic disease, or renal disease, which may produce malnutrition at this age. There may be other anomalies like congenital heart disease, which in a subtle way prevents adequate development.

Physical examination revealed a child who had failed to gain, had decreased in weight, had not increased very much in length, and was far below the third percentile. The physical examination is fairly nonrevealing. Except for a small, pale, and malnourished child we have little else to go on pointing to the diagnosis. There was marked wasting, and little subcutaneous fat. The baby, interestingly enough, was alert and took her feedings well. The tongue was reportedly smooth. I know that in several series of anemia in children, in which the tongue has been specifically inspected, the findings are rather disappointing in comparison to adult patients with the same degree of anemia.

The erythrocyte indices figured are: mean corpuscular hemoglobin, 50 micromicrograms, the normal being 27 to 31; the mean corpuscular volume 150 cubic microns, the normal being approximately 81 to 91. So we have constants that are far above normal and point to a highly macrocytic type of anemia. These indices, even if one considers that the red count may have been wrong, are most unusual, even in a severe megaloblastic anemia at this age, and yet I think that we can be reasonably sure that we are dealing with a macrocytic anemia.

Uniform macrocytosis at this age is unusual because a severe degree of folic acid deficiency has not been present long enough to allow for a shift in the marrow back to the more primitive forms and also an alteration in those primitive forms to the typical large cells called megaloblasts. It is actually very difficult to make a diagnosis of megaloblastic anemia, or macrocytic anemia, in a baby this young on the basis of the peripheral smear, because one sees a large number of small cells intermingled with macrocytes. With the large number of small cells that are present, the mean corpuscular hemoglobin and the mean corpuscular volumes are brought down so that one cannot use the constants as a guide.

The gastric acidity showed 4 units of free hydrochloric acid, and I do not know whether or not that was following histamine. It probably was, and it was low. This is another feature that has been popularized in regard to its occurrence in megaloblastic anemia. Actually, the hypochlorhydria returns to normal after therapy and is a temporary thing in contrast to the hypochlorhydria in typical pernicious anemia in adults. The bone marrow was said to be consistent with megaloblastic anemia.

An x-ray film of the abdomen on admission showed numerous fluid levels, with no selective distention, and preserved peritoneal lines. On speaking to Dr. Neuhauser beforehand, he believed that this was consistent or compatible with the degree of diarrhea that had gone on before and was not diagnostic and may be seen in other types of gastroenteritis or occasionally in sprue. Two days after admission the patient was started on folic acid by mouth, 100 mg. per day, and the next day ascorbic acid, 100 mg. per day. Folic acid in this dose is much more than enough, it is a very high

dose, and yet I think that one can be justified in giving folic acid orally in this dose, even to a patient with gastroenteritis. I think more often it is given parenterally but I think with this dose certainly a patient with this degree of gastroenteritis, and even a more severe degree of gastroenteritis, will absorb enough folic acid for a response. These drugs were continued throughout admission, and I see they were given parenterally after nine days. It probably was given parenterally because there was no appreciable response to it orally.

The only two points that I would like to make in regard to the therapy here brings me back to the two horses that I have always ridden, at least during residency days. One is the use of skimmed milk formula in a patient who is on borderline dehydration and who has diarrhea. It has been pointed out for many years that skimmed milk formula with its very high protein content creates a high renal tubular load and obligatory water excretion in order to get rid of that nitrogenous load, so that even a normal patient with such a diet is on the brink of dehydration. I think it is better to increase the calories with carbohydrates; then we have a more physiologic mixture. The other point is the use of penicillin in a patient 3 months of age in which infection is being considered. We do know that the type of organism we are dealing with in a newborn infant, or an infant during the first year or two of life, is not only the gram-positive coccus, but often the gram-negative bacillus, and, therefore, if one is considering adequate coverage in regard to antibiotic chemotherapy, I think it is always well to include a drug that will be effective against the gram-negative organism. I think it would have been well to give a sulfa preparation, as this was back in 1947, as well as penicillin; at that time Gantrisin and other soluble sulfonamide compounds were available. On the institution of folic acid and vitamin C therapy, the hemoglobin ranged from 7.8 to 8.3 to 9.25 Gm. Thus, in nine days with oral folic acid we have a rise of only 1.5 Gm. of hemoglobin, and this is far below what one expects in a case in which there are no other types of complication, and even in most of the patients with other infections or gastroenteritis there is a response of anywhere from 0.2 to 0.3 Gm. of hemoglobin per day following the institution of therapy. We have further evidence that there was lack of response, or incomplete response, to folic acid, in that the reticulocytes reached a high of only 6.4 per cent six days after folic acid therapy. With an initial level of 7.8 Gm. of hemoglobin and 1.6 million red count, one would expect a reticulocyte count of at least 20 per cent if there were no complications. The white count rose to 21,000, with a marked shift to the left, and it finally fell to 11,000. One can see leukocytosis even in a patient with megaloblastic anemia. Bleeding in a patient with megaloblastic anemia of almost any type is very rare. Actually it was commented on by Dr. A. Biermer[1] in his classic description of pernicious anemia in 1872 following Addison's description; he pointed to gastrointestinal hemorrhage, genitourinary hemorrhage, and retinal hemorrhage as possibilities. But certainly in recent years, and in the literature, it is an uncommon thing in spite of the

fact that the platelets are low. Occasionally one may find petechiae or purpura, but bleeding of the gastrointestinal tract, even to this degree, is most unusual in the usual megaloblastic anemia.

What are the possibilities? The patient certainly did not have thrombopenia except agonally. There is one other defect which might exist, and that is a deficiency of prothrombin. It is rather unusual to get just melena on the basis of hypoprothrombinemia, and it is unusual to get it in anemia of infancy. Another possibility is that, with this persistent gastroenteritis, there were inflammatory changes in the mucosa of the bowel, erosion, and possibly small ulcers.

I think I can summarize the fluid given by stating that the patient in a period of thirty-eight hours received 210 c.c. of saline per pound, and 116 c.c. of dextrose and water per pound, which I think everyone will agree is a rather large amount of fluid, particularly the blood, the plasma, and the saline.

In summarizing the case from the point of view of the cause of death, there was a good deal of enthusiasm in regard to fluids. It is possible that the patient appeared that dehydrated and needed that much blood. However, we find a rise of hemoglobin all the way up to 15 Gm. and 3.96 million red count. As we have learned so many times before it is well to proceed carefully in replacing fluid and not to reinstitute complete restoration of fluid. The cause of death was probably pulmonary edema. There may well have been pneumonia (which so often is found in a severe case of gastroenteritis), megaloblastic anemia, and congestion in other organs. In addition, the patient may well have died from a bacteremia or sepsis, and one of the factors may have been incomplete coverage so far as antibiotics are concerned. Possibly the antibiotic just was not the correct one for the type of organism or bacteremia that resulted. So we have those two possibilities as the cause of death—pulmonary edema and possibly sepsis or bacteremia.

Regarding the megaloblastic anemia, probably that is one of the most important points of this whole discussion. It presents a number of unusual factors. One is the fact that the platelets were normal, except agonally. But even more important is the fact that the patient did not respond to folic acid. On checking over the reticulocyte counts even after parenteral folic acid in the four-day period that the patient lived, there was no appreciable reticulocytosis, so that it is unlikely that folic acid was effective by either route. Folic acid will convert megaloblastosis of any etiology to normal, at least initially. This holds true also of pernicious anemia. In trying to comb any possibility whereby folic acid may not be effective in the presence of megaloblastic anemia, two things come to mind. First is a patient whom we recently have seen and who has been reported in the literature with erythremic myelosis, a type of leukemia characterized not only by abnormality in the white cells but also in the red cells. This probably is on the basis of the fact that even though folic acid is available it does not enter into the enzyme system. The other possibility is the megaloblastosis that one oc-

casionally sees in patients with hypoplastic or aplastic anemia, particularly of the so-called Fanconi anemia type. This Fanconi anemia is an aplastic anemia, which is associated with other congenital anomalies. It has been observed many times that the anemia reverts to a macrocytic type, and then finally a megaloblastic picture, and there is again no response to folic acid and vitamin B_{12}. We may here again have another instance whereby there is some abnormality in the actual enzyme system, so that even though folic acid is available, it is not utilized. But other than that, I know of no instance whereby the megaloblasts may not be reverted.

Folic acid deficiency is probably almost always the cause of megaloblastosis in infancy. There are many factors, and I think all of them play a part in any given case. An inadequate intake—milk, for instance, which is the principal food during the first few months of life and the first year, is very low in both B_{12} and folic acid. Decreased bacterial synthesis induced by antibiotics is a factor. We have seen megaloblastosis in the marrow of patients who have been on Aureomycin and penicillin for long periods of time, so that this was probably due to decreased synthesis in the bowel. It may have been a type of bacteria that actually used up or destroyed the folic acid, and so megaloblastosis may have resulted. Increased metabolic requirements as in infection, failure of absorption in sprue, and failure of utilization by simultaneous deficiencies of vitamin C or B_{12} may give rise to a megaloblastic marrow. Although vitamin C is known to enhance the conversion of folic acid or folinic acid, it is not necessary in all cases. If it is deficient, it will increase the severity of the megaloblastic anemia or allow it to develop much quicker; but actually it is not necessary for the conversion of folic acid or folinic acid.

Finally, of course, rapid growth, as in premature or newborn infants, will make manifest deficiencies much more quickly. Folic acid or B_{12} will convert a megaloblastic anemia within forty-eight hours from megaloblastosis to a normoblastic marrow, so that there should be readily available evidence two days after the preparations are given. We have, then, megaloblastic anemia probably due to folic acid or B_{12} deficiency, and gastrointestinal bleeding probably due to inflammatory changes, erosions, or possibly to ulcers. Again a premature infant, who has been given suboptimal amounts of vitamins—though given large amounts of vitamin C because of infection and other complications—may have some evidence, even though it is not clinical, maybe microscopic, of scurvy or rickets.

DR. SIDNEY FARBER.—Thank you, Dr. Apt. Dr. Neuhauser, do you have anything you would like to show us at this time. Any discussion of your findings by x-ray?

DR. E. B. D. NEUHAUSER.—There was no evidence of scurvy by x-ray.

DR. FARBER.—Dr. Diamond, do you wish to discuss the problem?

DR. LOUIS K. DIAMOND.—I would like to mention that not all the patients we see fit into the categories that are pure folic acid deficiency, due to vitamin B_{12} deficiency, or completely normal. In other words, they are not all black or white. There are too

many grays, and the number of patients with mixed deficiency, with failure to respond as they should respond if they were pure cases, is so much larger than those we see with the pure deficiency that we are constantly distressed and unable to account for the disturbances. We are impressed particularly by the role of infection, not only in the development of these hematologic changes, but also in the failure of response. I think even as far back as 1927 and 1928, Dr. Minot pointed out that an active preparation of liver given to a patient with pure pernicious anemia would not necessarily produce a favorable maximum reticulocytosis if the patient had an infection at the time. In the same way we are impressed by the number of children who may have infection predisposing to the development of this hematologic picture, or even if it is secondary, and in whom the response to this specific principle is not good in the face of infection.

I think Dr. Matthews might give us just a brief run down of the bone marrow findings, and also the brother's picture, which was not as simple as the record seemed.

DR. SANFORD MATTHEWS.—Examination of marrow on this child, done on the day of admission to the hospital, showed definite changes in the nuclear patterns. These were consistent with the presence of megaloblastic changes, not such as you would see in a completely relapsed pernicious anemia, but rather in a partial or an incomplete deficiency of whatever hematopoietic factors were absent. These changes were manifested primarily in the white cells, with large macropolymorphonuclear leukocytes, band forms, and metamyelocytes. There were also suggestive changes in the red cells. These changes were not categorical, however, and I am sure that there would be some argument about them.

The sibling's feeding was similar to the patient's. This child was seen here at 4½ months of age. The feeding had consisted principally of the same commercially prepared formula with added orange juice up until the age of 4 months, at which time it was changed to evaporated milk and water, ostensibly because of some diarrheal problem and failure to do well. The child was seen here 2 or 3 weeks after having been placed on this evaporated milk formula. At that time, examination of the marrow showed changes indistinguishable from those of his sister. His hemoglobin at that time, however, was 10 Gm., and his reticulocyte count 4.3 per cent. The child, in view of the alarming course that his sibling had taken, was also admitted to the hospital, and he was begun on both oral and parenteral folic acid in sequence. The reticulocyte rise was never remarkable; however, it did climb to 7 per cent on one occasion. The hemoglobin had a concomitant rise to about 11.5 Gm. The child ran a desultory course, with persistent diarrhea, which was not as severe as that of his sibling. He continued to have an upper respiratory infection, which smoldered on and eventually cleared. During his hospital stay he gained about 1½ pounds. The hemoglobin returned to normal; there was a reversion of a latent macrocytic pattern in the peripheral blood to a relatively normocytic pattern.

DR. FARBER.—Thank you, Dr. Matthews. I will ask Dr. Craig to give the post-mortem findings.

DR. JOHN M. CRAIG.—This was a rather small child and most of the organs were about one-third normal weight, with the exception of the lungs, which were increased in weight. There was no peripheral edema, although there was free fluid in the peritoneal cavity, and 30 c.c. in each pleural cavity. There was a large amount of edema fluid in the retroperitoneal tissues, in the mesentery, and in the omentum, so that the child was regarded as being considerably overhydrated. The lung showed considerable congestion, some edema, and an early bronchitis. In the stomach, there were small ulcerations; in the duodenum, a similar small ulcer was found; and small ulcerations were also found in the small intestine, microscopically. In the ileum, the inflammation extended down into the submucosa, so that there were actual inflammatory ulcerated erosions, fairly widespread, through the small intestine. It is believed that, in part, the hemorrhage had come from these areas. There was considerable evidence of malnutrition; the fetal fat was depleted. The lymph nodes showed not only considerable depletion of lymphoid tissue, but widespread separation of the sinusoids, indicating the tremendous amount of edema that was present. There was shrinkage of the cells in the liver and some hemosiderosis in the parenchymal cells of the liver also. There was no extramedullary hematopoiesis, however. The bone marrow was very hyperplastic (Fig. 1), with a large number of uniformly appearing cells,

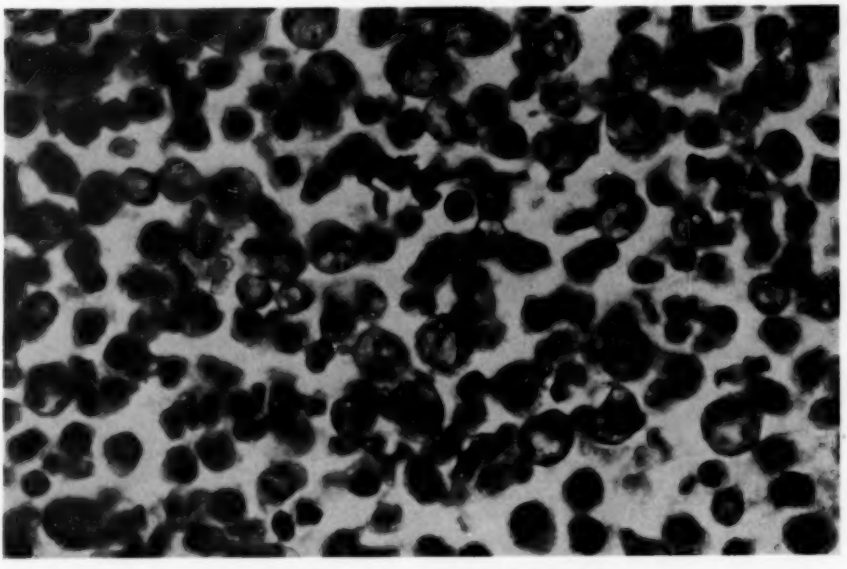

Fig. 1.—Vertebral bone marrow. Many large immature erythroid forms are seen in a hyperplastic marrow. (Hematoxylin and eosin; ×870.)

which, in our opinion, represent quite early erythroid forms, probably somewhere in the erythroblast stage. They did not show, I believe, the typical megaloblastic character, because their cytoplasm was rather on the small side, but there was definitely an arrest in the development of the erythroid cells at an early and primitive level. There were almost no megakaryocytes present, and survey of all sections of bone showed that absence to be quite uniform.

The immediate causes of death in this case were: (1) the factor of severe generalized edema due to increased fluid administration, (2) hemorrhage into the bowel as a result of ulceration in relation to her primary diarrheal disease. The bleeding tendency, I think, was certainly increased by the probable decrease in the number of platelets resulting from the comparative absence of the megakaryocytes in the bone marrow. We do not believe that the child had sepsis. The bone marrow is believed to represent a regenerative hyperplastic marrow, with a partial failure of maturation of the erythroid series, probably due to a partial failure of folic acid or B_{12} metabolism, but not representing a true full-blown picture of megaloblastic anemia. The cause for the great decrease in megakaryocytes was not apparent, but the decrease undoubtedly accounted for the terminal thrombocytopenia.

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Medical Progress

PRESENT STATUS OF THE CELLULAR AND HUMORAL THEORIES OF ANAPHYLAXIS

KENNETH L. BURDON, PH.D.
HOUSTON, TEXAS

NOTWITHSTANDING a great volume of research in the field, scholars are still not agreed upon any one comprehensive explanation for allergic phenomena. Indeed, the immensity and complexity of the problem have become ever more apparent. While there are some who picture manifestations of hypersensitivity, and associated refractory states, as dependent solely upon specific interaction between antigens and antibodies, other investigators look to the still incompletely understood nonspecific biochemical changes in the sensitized animals, after the primary antigen-antibody combination, as the area in which significant answers to the underlying mechanisms are likely to be found. Chase[27] recognizes the probable importance of nonspecific factors when he says: "Certainly there are operative mechanisms in allergic reactions that are not readily interpretable in terms of experience with known antigen-antibody systems." The complexity of the phenomena to be considered is illustrated by the occurrence of both the so-called *immediate type* of reaction (e.g., systemic anaphylactic shock, asthma and hay fever, wheal and flare and Arthus varieties of skin reactions) and the *delayed* (tuberculin) type of response. In this review we shall be concerned principally with the former, since the delayed reactions present special problems which could not possibly be discussed adequately.

The theoretical concepts most widely accepted at the present time are embodied in the so-called *cellular histamine theory*. Originating in the observations of Friedberger[51] and other early workers, and greatly strengthened and enlarged by Dale[35] and collaborators, this theory has enjoyed almost universal support for the past quarter century. Topley and Wilson[114] state this concept as follows:

"The balance of experimental evidence is strongly in favor of the view that the anaphylactic response is the result of an antigen-antibody reaction occurring on or in the cells that have removed the antibody from the blood and in some way fixed it themselves. The anaphylactic state is associated with the presence of fixed antibody and the absence of circulating anti-

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body, though in the rabbit, and occasionally in other animals, the white cells of the blood themselves are sensitive to shock. The immune state is associated with the presence of circulating antibody in a concentration sufficient to protect the fixed antibody that is also present.

"The difference between the anaphylactic and immune state is quantitative rather than qualitative, depending upon the balance between circulating and fixed antibody."

Kállos[65] reaffirms the cellular view, with particular reference to clinical allergy in man: "First and foremost, in all types of allergy only the antibodies affixed to tissue cells are of importance in eliciting allergic reactions. There is nothing to prove that circulating antibodies participate in these reactions."

In explanation for the state of anti-anaphylaxis and the phenomenon of specific desensitization (or hyposensitization) the proponents of a strict cellular theory stress the postulated protective effects of circulating antibodies, especially antibodies of the so-called "blocking" type, and hold that all successful methods of producing a refractory state depend essentially upon preventing rapid combination of antigen with any considerable number of fixed ("sessile") cellular antibodies.

An added component of the theory, much emphasized in recent years, is the role in the actual production of symptoms attributed to chemical mediators of shock, especially histamine. The primary event in initiating an anaphylactic reaction is said to be a special type of cellular injury, causing release from the cells of preformed histamine, histamine-like substances, and other metabolites, including acetylcholine and heparin, which in turn produce contraction of smooth muscles, changes in capillary permeability, and other pathologic changes of anaphylactic shock. The belief that the *cellular site* of the antigen-antibody combination is the crucial feature of hypersensitivity is so widely held that it may be said to permeate virtually all current literature in this field, and is generally accepted as a point beyond question.

The present dominance of this cellular view, however, has not eliminated entirely another concept which receives at least passing mention in current discussions of hypersensitivity. This is the *humoral theory*, which would give primary importance to anaphylactogenic poisons ("anaphylatoxins") supposedly formed *in the body fluids* as a consequence of antigen-antibody union there.

Friedemann[52] mixed in a test tube an antigen and its homologous antiserum (red blood cells and specific hemolytic amboceptor) in the presence of complement, incubated the mixture for a short period, then just before the onset of hemolysis injected the supernatant fluid intravenously into normal rabbits. The animals died with symptoms resembling those of anaphylactic shock.

Friedberger[51] repeated and extended these experiments. He collected the precipitate obtained by the in vitro mixing of antigens and their antisera, then added the washed precipitate to fresh normal guinea pig serum, and after a brief period of incubation, inoculated the supernatant into normal guinea pigs. The injected material was found to have marked toxicity, causing in the guinea pigs an

acute shock like that characteristic of specific anaphylaxis. Friedberger suggested that the antigen-antibody complex absorbed to itself from the guinea pig antiserum a proteolytic ferment, which by its digestive activity caused the appearance of an anaphylactogenic poison.

Thus, the humoral theory began with the appealingly simple idea that the combination of antigen with specific antibody in the blood, or other body fluids of the hypersensitive subject, initiates a rapid change resulting in the appearance of a potent poison, a so-called anaphylatoxin.

A strictly humoral concept of anaphylaxis failed to win general acceptance, however, for a variety of reasons, some of which will be discussed below. Instead, the humoral theory became a forgotten cause, especially after Dale[33, 35] showed conclusively that the isolated uterine tissues of sensitized guinea pigs would exhibit a typical anaphylactic response even after they had been washed and perfused free of blood. So the matter stood until the past few years, during which a revival of interest in the probable role of humoral factors has occurred.

This seems, therefore, an appropriate time to re-examine critically this once-favored humoral-anaphylatoxin theory, and also to reappraise the adequacy of the evidence for the concept which most strongly influences current thinking, the cellular-histamine theory. In seeking more adequate explanations of the complex phenomena of hypersensitivity it is obviously important first to understand the limitations and inadequacies, as well as to recognize the well-validated contributions, of these older classical theories.

THE CELLULAR-HISTAMINE THEORY

The belief that antibodies fixed to tissue cells are exclusively concerned in allergic reactions got an early start and still derives much of its support from conditions surrounding the passive transfer of hypersensitivity in guinea pigs, specifically from the fact that in this species a period of time ("incubation or latent period") is ordinarily observed after an animal has been injected with antiserum before the introduction of the shocking dose of antigen will elicit the maximum anaphylactic response. Except for this circumstance the early investigators were prepared to believe that the circulating blood furnished the ideal situation for the underlying antigen-antibody reaction in anaphylaxis, since it was generally recognized that in a sensitized animal, of whatever species, the most certain and effective way to produce the maximal response was to inject the antigen intravenously. But if one chose the animal apparently most suitable for showing shock, namely, the guinea pig, and inoculated into the veins the antibody-containing serum from a sensitized animal, only after the passage of about two hours would the injection of the antigen regularly produce any noticeable symptoms, and the acutely fatal anaphylactic shock would not occur until after a minimum of four to six hours, by which time most of the injected antibody would have disappeared from the blood stream. This seemed to prove that the combination of antigen and antibody in the circulating blood did not involve injury to the body, whereas union of the antigen with the antibody which had become attached to the cells *did* bring about anaphy-

lactic shock. The latent period was therefore assumed to be the time necessary for the injected antibodies to be taken up by the tissue cells.[42, 76, 122]

It cannot now be maintained, however, that the latent period, as ordinarily observed in the passively sensitized guinea pig, is truly *essential* for the production of all anaphylactic reactions by passive transfer, either in the guinea pig or in other animal species.

Passive anaphylactic reactions produced by the injection of antigen immediately after a sensitizing dose of antiserum, i.e., *without* an incubation period, were early observed in the *rabbit*.[52, 104] The lack of necessity for a latent period in passively sensitized *dogs* was indicated in the experiments of Manwaring and associates[81] and more definitely by Sherwood and coworkers,[107] who obtained immediate anaphylactic shock by intravenous injection of antigen and antibody simultaneously, or after mixing. In recent quantitative studies Dulaney and associates[47] varied the interval between sensitization with a constant quantity (21 mg. AbN) of rabbit antiserum and the administration of the shocking dose of antigen from three and three-fourths to thirty-six hours. They found no correlation between the length of this interval and the size of the antigen dose required for severe or fatal reactions. Unfortunately no tests with a waiting period shorter than three and three-fourths hours were made.

Early workers believed that passive anaphylaxis could not be produced at all in *mice*, since animals presumably sensitized by an injection of antiserum did not react when the specific antigen was inoculated after the usual incubation period of twenty-four to forty-eight hours. It has since been reported[23] that when both antiserum and antigen are injected, *one right after the other*, intravenously, severe or fatal anaphylactic shock occurs; typical shock thus may be regularly produced, whichever reagent is injected first. These reactions were specific, and like those of active anaphylaxis in mice.[22] They apparently resulted from antigen-antibody combination in the circulating blood, and did not involve an incubation period. Solotorovsky and Winsten[108] obtained definite anaphylactic reactions or deaths only occasionally among mice passively sensitized by the intravenous injection of homologous or heterologous (rabbit) antiserum, when the animals were challenged by intravenous antigen injections two to forty-eight hours later. Even though the rabbit antibovine albumin serum contained 0.6 to 0.7 mg. AbN/ml it did not appear to sensitize regularly against an antigen dose of 1 mg. albumin. However, the authors did not test the effect of an intravenous injection of antigen immediately after the antiserum.

Most significantly, passively sensitized *guinea pigs* also have been found capable of reacting typically, though not with the same regularity as animals of other species, to an injection of antigen almost immediately after a sensitizing dose of antiserum, as well as when these two reagents are introduced in reversed order.[59, 72] Zinsser and Enders[125] reported that, although they thought it "probably exceptional," "guinea pigs may develop acute, often fatal, typical anaphylactic shock when injected intravenously either with antigen followed by sufficiently

potent antiserum, or vice versa, within one-half to ten minutes." Dean and collaborators[41] found that of seventy guinea pigs receiving an intravenous injection of antigen immediately (three to five seconds) after introduction of rabbit antiserum, thirty-eight (54 per cent) died of acute anaphylactic shock, while most of the remaining animals showed delayed anaphylactic symptoms. On the other hand, *all* of the fifty-eight control animals given the same shocking dose of antigen after the usual twenty-four-hour waiting period died in acute shock. These findings illustrate the *greater regularity* of results in guinea pigs when the usual incubation period is allowed, but at the same time they again show that, at least with relatively large doses of the reagents, such a latent period is not a necessary part of passive anaphylaxis, even in the guinea pig.

This matter has recently been reinvestigated in a definitive way through the quantitative studies of Kabat and his colleagues,[84] and others. Benacerraf and Kabat[9] found that in guinea pigs the latent period of passive sensitization is an inverse function of the sensitizing dose of antibody. A fatal, severe, or moderate anaphylactic shock was produced in guinea pigs sensitized with 2 mg. of AbN when the antigen was injected immediately. When a thirty-minute interval was allowed, only 1.02 mg. of antiovalbumin nitrogen was required to bring about uniformly fatal anaphylaxis with the same dose of antigen. After five hours' interval only 0.06 mg. AbN was needed. Thus, the sensitivity of the guinea pigs clearly increased as the injected antibodies had time to permeate the tissues. It was also shown that as the interval between sensitization and shock was lengthened, a given quantity of antibody sensitized more fully. The authors suggest that during the interval a reaction of some kind occurs which may well be the fixation of the antibody upon the cells. However, unquestioned anaphylactic reactions *did* occur when injection of antigen followed inoculation of antiserum immediately, and the writers state that the necessity for actual cellular fixation of the sensitizing antibodies remains an assumption.

In connection with the induction of transient local skin reactions in normal guinea pigs and rats by the intradermal inoculation of antiserum, followed two to six hours later by the intravenous injection of antigen plus a dye (passive cutaneous anaphylaxis), Ovary[89, 90] has reported findings similar to those of Kabat and Benacerraf. He concluded that an "incubation period" is necessary for the full development of this reaction, just as in the case of systemic anaphylaxis. The dependence of the reaction upon the quantities of antigen, as well as antibody, available at the skin site is apparent, however, and in this connection the observations of Benacerraf and associates[8] may be pertinent. They showed that if a small amount of histamine, or other mild irritant, is injected locally in the skin immediately after the intravenous inoculation of antiovalbumin serum, the antibodies from the circulation accumulate rapidly at this site, so that a strong passive cutaneous reaction may be elicited at that place by intradermal introduction of a minimum quantity of antigen as early as two hours later; otherwise

the skin would not become sensitive to this antigen dose for twenty-four hours. This apparently is a reflection of the ordinarily slow passage of injected antibodies from the blood to the skin,[49] unless their accumulation at a particular spot is accelerated by a local increase in capillary permeability or by cellular injury. Actual "fixation" of the antibodies to the skin cells may not be involved.

Turning now to the Arthus phenomenon, which appears to be a composite reaction, having elements of both the immediate and the delayed type of tissue response,[57] we find universal agreement that this manifestation of hypersensitivity can be regularly induced in guinea pigs, as well as in rabbits, without an incubation period, and by the reverse as well as by the ordinary passive transfer method. Moreover, the dependence of the reaction upon circulating antibody has been stressed by all observers.[10, 91]

The regular success of the *reversed* passive transfer techniques would seem to be of crucial significance. Since the symptoms occur immediately after introduction of specific antiserum there would seem to be no opportunity for the injected antibodies to become fixed to the body cells before the reaction begins. Reversed passive anaphylaxis in guinea pigs has been described by Kellett,[72] Zinsser and Enders,[123] Van den Ende,[118] Swineford,[111] and others. Ovary[90] reported failure to obtain passive cutaneous reactions in guinea pigs by the reversed procedure, but Bier and Siqueira,[13] using similar quantitative techniques with a protein (rabbit gamma globulin) antigen, obtained positive results. Reversed passive sensitization of the human skin has been demonstrated repeatedly.[66, 124]

The production of anaphylactic reactions by injection of antigen-antibody *mixtures* into normal animals has been reported by numerous investigators. Most recently Braune[16] has pointed out the promptness with which anaphylactic symptoms appear after injection of suitable mixtures, and the unlikelihood that introduction of these preformed complexes involves any cellular fixation of antibodies.

Taken together, the considerations discussed above would seem to throw considerable doubt upon the traditional assumption that "sessile" antibodies, anchored to the cells, are necessarily and exclusively involved in all hypersensitivity reactions, and instead would seem to validate the conclusion of Opie[87]: "It is unnecessary to assume that the tissues of an animal are sensitized by either antigen or antibodies to the action of the other."

It is true that the almost instantaneous contraction of the washed uterine strip, excised from a sensitized guinea pig, when specific antigen is added to the bath in which the muscle is suspended,[33, 35] remains a compelling example of an anaphylactic reaction occurring apparently exclusively at a cellular site, and in the absence of serum. The complete lack of free antibodies in the perfused smooth muscle preparation must remain uncertain, however, and in any case it does not necessarily follow that anything universal is illustrated here, or that antibodies in the circulation may not participate in, and contribute to, anaphylactic reactions in the whole animal. Freund and Whitney[50] found

that in passively sensitized *rabbits* antibodies introduced into the circulation require several hours to accumulate in the skin or uterus, but after seventeen hours they have penetrated so thoroughly that they can no longer be washed out by perfusion of these organs. This would seem to support the cellular theory, according to which the anaphylactic antibodies become fixed to the cells during the "incubation period" of passive anaphylaxis. But the further observation was made that these perfusion-fast antibodies could be removed merely by grinding the organs with sand and extracting with salt solution, suggesting that they were not firmly attached to the cells, if attached at all. The situation may be different, of course, in guinea pig tissues. It is also possible that in the guinea pig we have the exception, rather than the rule. With regard to both local and systemic anaphylaxis, it is reasonable to expect that the more thoroughly the antibodies have penetrated the tissues, and the more intimate is their contact with the interstitial and intracellular tissue fluids when they interact with antigen, the more marked will be the manifestations of cellular injury.

As already indicated, the concept of the orthodox cellular theory regarding the role of circulating antibodies is another feature which invites critical analysis. Of particular interest in this connection are the experiments of Weil, in which he attempted to show that sensitized guinea pigs could be protected from anaphylactic shock by deliberately flooding their circulating blood with specific antibodies just prior to the injection of the shocking dose of antigen. These studies have been widely quoted, and almost universally have been given great weight as proof of the protective action of antibodies in the blood. (See, for example, the text and diagram in Topley and Wilson,[114] page 1147.)

Weil found that "the successful issue of this experiment waited upon a large number of futile trials."[121, 122, p. 515] He was obliged to use relatively large amounts of rabbit antiserum, up to thirty to thirty-five sensitizing doses (3.0 to 3.5 ml.), before some of the animals were protected against fifteen lethal doses of antigen. The protocols of these experiments show a total of only five sensitized guinea pigs, supposedly protected by an excess of specific circulating antibodies, that actually survived the test injections, and all except one of these had some anaphylactic symptoms. In further trials, using the serum of immunized guinea pigs, he commented again about technical difficulties, then presented a protocol summarizing "the outcome of the most successful series." This protocol lists only four guinea pigs which were injected with immune guinea pig serum just prior to inoculation of the shocking dose of the antigen. Of these, three survived (two after mild, and one after severe, symptoms), while the fourth animal died of anaphylaxis. Despite these meager positive findings, Weil concluded that "the function of immune bodies present in the serum is to neutralize the introduced antigen, and so to protect the body cells." In explanation for the finding that the minimal protective dose of an immune serum must be thirty or forty times the sensitizing dose of such a serum, he postulated that the cell-anchored antibodies have a greater avidity for

the antigen than the free antibodies in the blood.[121]

There can be little doubt that Weil's interpretation of his few positive results was mistaken. Later, he reported that after sensitization had been established passively in guinea pigs, the sensitive state could be "terminated" by the injection of large doses of certain lots of *normal* rabbit or *normal* sheep serum.[121] These later findings are consistent with those of several other authors who have reported that normal heterologous serum may inhibit anaphylactic reactions when introduced into the circulation preceding the test injection of antigen. Morris[84] showed that normal rabbit or guinea pig serum, containing no specific antibodies, when introduced intravenously before testing with antigen usually sharply reduced the reactivity of the sensitized guinea pig. On the other hand, the injection of a rabbit antiserum containing many of the specific antibodies tended to enhance sensitivity. Morris further demonstrated that specific desensitization is not necessarily accompanied by any appreciable reduction in the amount of circulating antibodies, and is not dependent upon the quantitative distribution of cellular and humoral antibodies. She concluded that: "An excess of antibody in the circulation does not establish a state of anti-anaphylaxis. On the other hand, some protection against anaphylactic shock may be induced non specifically merely by the introduction of serum, whether containing the specific antibody or not."

Similar observations are described by Von Fennyvessy and Freund,[120] Karsner and Ecker,[67] Kellaway and Cowell,[70] Hill and Martin,[61] and Teale.[112] Baserga and Bergamini[7] concluded that in guinea pigs "the amount of circulating antibodies in the serum does not seem to be of any importance in determining the state of hypersensitivity or refractoriness in anaphylaxis provided that the shocking dose of antigen is in the region of antigen excess."

To the evidence already known implicating antibodies in the blood as the cause of symptoms in other species, data have been offered recently indicating that systemic anaphylactic reactions in actively sensitized *chickens* are mediated through circulating antibodies.[80]

Further weaknesses in the cellular theory are revealed when its explanations for the process of desensitization and for the antianaphylactic state are examined. The differing mechanisms suggested cannot be resolved into one harmonious concept. If "neutralization" or "saturation" of the sessile antibodies by antigen injections is responsible for desensitization, as the theory claims, then these anchored antibodies must have greater avidity for the injected antigen than do the free antibodies in the circulation, as indeed Weil was forced to assume. Now if, as the theory also says, the refractory state depends in other circumstances on the protective effect of antibodies in the blood stream, then in these conditions an opposite assumption must be made, namely, that antigen combines preferentially with circulating, rather than with cell-fixed, antibody.

These contradictions and other aspects of the problem of the mechanism of desensitization have been cogently discussed by Bronfenbrenner.[18-20] He concludes: "The temporary relative refractoriness of a hypersensitive animal, achieved through the administra-

tion of a suitably chosen dose (either single or multiple) of antigen . . . . . is secured by neither the interposition of circulating antibody between the antigen and sensitive cell, nor by the saturation of fixed antibodies. Apparently the refractoriness is determined by some other mechanism entirely outside of antibody balance."[20]

Consideration needs to be given, however, to newer knowledge of special forms of antibodies.[24] Studies have revealed that a complexity and variety of antibody types, differing in thermostability, avidity, and diffusion rate in the tissue, yet all having specific affinity for the antigen, may be involved in hypersensitivity. These include besides ordinary (complete) precipitating antibodies, at least two types of incomplete (nonprecipitating or coprecipitating) antibodies, the so-called *blocking antibodies,* and the *reagins,* both of which may be present in the same serum.[56, 82, 92, 96]

The *reagins* present in the serum of persons showing the immediate type of allergic reactions are characterized not so much by their incompleteness, as by their persistence in the tissues where they are injected, in contrast to the blocking antibodies which diffuse away. Thus reagins, which evidently may be responsible for the primary reaction with antigen leading to symptoms in common forms of human allergy, and also in systemic anaphylactic shock, are generally thought of as closely associated with the tissues, perhaps attached to cells. Their role in hypersensitivity is generally interpreted as supporting the basic tenet of the cellular theory.

Evidently there is nothing necessarily protective about incomplete antibodies, as such. Incomplete coprecipitating antibodies have been shown to be as effective as complete antibodies for the passive sensitization of guinea pigs[9] and they certainly participate in skin reactions and other clinical forms of allergy in man.[78]

In 1935 Cooke and associates demonstrated[31] in the serum of *treated* hay fever patients the "peculiar blocking or inhibiting type of immune antibody." They found that the injection of a mixture of the serum from a treated ragweed-sensitive patient and ragweed pollen extract into the skin of a normal person failed to cause a local reaction, whereas injection of a similar mixture of the serum from an untreated patient and the pollen extract was followed by a skin reaction within thirty to sixty minutes. The subject was further pursued by Cooke and co-workers,[30] and by Loveless and colleagues,[77-79] who believed that the inhibiting effect of treated patient's serum was due to a true antibody which caused a specific "inactivation of the antigen." A rise in the titer of the blocking antibody was demonstrated in human beings during specific hyposensitizing treatment, and Loveless reported that a parallel appeared to exist between the amount of the inhibiting element in the blood of her patients and in their relative degree of clinical insusceptibility. Subsequent studies, however, failed to bring unequivocal evidence for a clear correlation between blocking antibody titers and clinical improvement. Alexander and associates[4] concluded: "The mechanism by which clinical improvement occurs following specific pollen therapy remains unknown," and Cooke[30] stated: "Possibly . . . (the blocking antibody) . . . is a factor in

clinical immunity, but in view of what has been said I do not think there is yet sufficient proof that it is the most important factor. . . . Evidence has been submitted to show that there is some other unknown mechanism of immunity, which operates in the complete absence of demonstrable blocking antibody."

The effectiveness of blocking antibodies as protective factors against allergic reactions is probably limited. Certainly, the phenomenon of anti-anaphylaxis in general cannot be attributed principally to the blocking antibodies. For one thing, a state of relative refractoriness can be established in hypersensitive animals or human beings within a few minutes, or hours, after suitable antigen injections—a period entirely too brief for the production of any appreciable amount of new antibodies, and, moreover, the desensitization is just as promptly fortified by each succeeding injection.[19, 20]

Furthermore, an attempt to explain desensitization solely on the basis of the number or location of available specific antibodies of whatever type would have to ignore the evidence which points to an important role for *nonspecific factors* in the refractory state. The inhibitory effect of injection of normal heterologous serum has already been discussed. Maunsell[83] used two preparations for skin tests with naturally sensitized human subjects: (1) a mixture of extracts from pollens and fish, and (2) a mixture of feather and flour extracts. These allergens, in increasing concentrations, were repeatedly injected intradermally at separate sites into patients showing reactions to both of them until the respective skin areas were thoroughly desensitized; then careful, reciprocal cross-sensitivity tests were performed. Also, skin areas in a group of patients were desensitized with preparations containing amounts of one of the allergenic mixtures capable of producing weak skin reactions only, and a concentration of the other allergenic extract giving strong skin reactions. It was found that the different allergens having approximately equal skin reactivity in a particular patient desensitized the skin for each other. When one allergen was stronger in skin-reacting potency, it desensitized against itself and also against a weaker allergen. but the reverse was not true.

Chase[26] noted that when a severe allergic reaction was induced in guinea pigs with a simple chemical as antigen, the involved skin area not only failed thereafter to react to a second testing with the same antigen, but to a different antigen-antibody system as well. Bowman and Walzer[15] and Alexander and associates[2] have described temporary nonspecific local refractoriness following whealing reactions and urticaria in the human skin.

Higginbotham[60] studied the heterologous allergic reactivity of tuberculous guinea pigs desensitized by repeated injections of tuberculin. He showed that such animals not only lost their specific reactivity to tuberculin, but also exhibited simultaneously a marked reduction in their original sensitivity to several other bacteria.

Responses of excised smooth muscle from guinea pigs sensitized to more than one substance have been found to depend upon the order in which the different antigens are added to the tissue bath. When the better antigen is added first, the reaction to a second antigen is definitely weaker, or ab-

sent.[25, 33] Dale and Hartley[38] observed that the smooth muscle from guinea pigs sensitized to each of three different proteins of horse serum was desensitized to the other two after a strong reaction to any one of them.

It is surely not without significance, furthermore, that a refractory condition in sensitized men and animals can be produced deliberately by a great variety of entirely nonspecific means,[21, 58, 61, 98] and also that varying degrees of desensitization toward existing allergies are commonly observed to occur naturally in connection with intercurrent infections, fever, trauma, and other disturbances of the normal body economy.[53-55, 94, 123] Thus the refractory state has a strong element of nonspecificity, a feature which the orthodox cellular theory fails to explain adequately.

Finally, there is universal agreement with the claim of the cellular theory that *histamine* may play an important part in manifestations of hypersensitivity, but at the same time various studies have demonstrated that histamine itself cannot be the sole, universal allergic poison, as is sometimes implied. The role of histamine has been the subject of many reviews.[29, 37, 43, 44, 106] Histamine shock does not duplicate quite all the features of systemic specific anaphylactic shock, or peptone shock. Histamine does not produce the Arthus reaction.[32] It probably plays no part in specific anaphylactic reactions in rats or mice.[69, 93, 95, 110] A normal rat uterus, unaffected by exposure to ordinary doses of histamine, nevertheless will respond by contraction to anaphylactogenic substances released from sensitized guinea pig tissues during anaphylactic shock.[25] A guinea pig uterine horn, repeatedly shocked by addition of histamine until it ceases to respond at all, may still contract when the specific antigen is added to the bath.[30] Authentic allergic manifestations may occur in the presence of active substances which can only be characterized as *histamine-like*. This designation apparently applies to the H-substance of skin wheals[2] as well as to the "histamine" of systemic anaphylaxis.[1] Most significantly, histamine does not desensitize tissues to a subsequent anaphylactic reaction in the same area, and the antianaphylactic state evidently results from a body reaction to something other than histamine itself.

Nevertheless the general concept, now embraced in the cellular theory, that allergic reactions, at least those of the immediate type, are brought about through the effects of chemical mediators, released (or formed) in the tissues as a consequence of the antigen-antibody union, seems to be a sound one, and likely to lead eventually to a full understanding.

There remain b a s i c unanswered questions—specifically, what are the mechanisms by which these active substances are released or formed, and why are they liberated in significantly toxic amounts in the sensitized but not in the desensitized (refractory) state?

THE HUMORAL-ANAPHYLATOXIN THEORY

The original anaphylatoxin theory of Friedberger fitted in well with the findings of Vaughan and Wheeler[119] on the toxicity of the intermediate products of protein decomposition, and with the experiments of Biedl and Kraus[12] and others who had demonstrated that peptone, when injected

intravenously into dogs or guinea pigs, will produce an acute reaction strikingly similar to specific anaphylactic shock.

When other investigators began to study the production of anaphylatoxin in vitro, however, it was soon found that animal sera can be rendered toxic by a variety of procedures in which neither antigens nor antibodies are needed. Thus, anaphylatoxins (serotoxins) potent for guinea pigs could be produced by incubating normal sera with kaolin, starch, talc, barium sulfate, inulin, or agar. These observations served to emphasize the remarkable resemblance between specific anaphylactic shock and that produced by anaphylatoxins, and by peptone and related naturally poisonous protein derivatives, but they failed to establish any clear connection between the artificial modification of serum which made it toxic and the anaphylactic reaction as seen in the living animal.

An explanation was suggested by Bronfenbrenner,[17] and by Jobling and associates,[63] who found that the interaction of antigen with antibody in a serum, *or* the absorbing effect of added particles of kaolin or starch, caused a sudden reduction in the amount of antitryptic substances present, and an apparently simultaneous activation of a proteolytic enzyme, so that the serum begins at once to digest itself. Bronfenbrenner showed that the early products of this autodigestion produced symptoms characteristic of anaphylaxis in normal guinea pigs. The possible role of proteolysis of serum protein constituents in the formation of anaphylatoxin in vitro was also recognized by Bordet and Zunz.[14] Novy and co-workers[56] established clearly that the toxic products, corresponding to the "anaphylatoxin" of Friedberger, developing on incubation of serum with agar, specific precipitates, etc., result from *changes in the serum itself,* induced only indirectly by adding foreign substances.

Just a few years later the papers of Dale and collaborators,[34-36, 39] describing the contraction of the sensitized, perfused (presumably blood-free) guinea pig uterus in the presence of the specific antigen, and emphasizing the apparently basic role of histamine in the reaction, seemed to eliminate anaphylatoxins from serious consideration, and led to the virtual eclipse of the humoral theory. No one has questioned the fact, however, that cell-free blood serum contains a matrix or precursor material which can be readily converted into an active anaphylactogenic substance by various treatments, including contact with specific antigen-antibody aggregates. Eventually, this often-confirmed phenomenon will have to find its true place in the pathogenesis of allergic reactions.

In the meantime a number of recent experimental findings may be cited which indicate a more active role of humoral factors in anaphylaxis than is generally appreciated.

In connection with the experiments[31, 77, 78] revealing the presence of blocking antibodies in the serum of treated allergic patients, it was at the same time demonstrated that mixtures of reagin-containing serum and of the specific pollen allergen would produce skin reactions in normal persons like those of ordinary Prausnitz-Küstner tests, except that they were slightly delayed. Somewhat earlier Foran and Lichtenstein[48] made a careful study of this phenomenon. They described the

reactions as minimal at fifteen minutes, much further developed at sixty minutes, and reaching a maximum at ninety minutes after injection of the mixtures into the skin. The authors recognized that these results could be interpreted as indicating the formation of a toxic skin-irritating product in the serum following the antigen-antibody combination there. They favored, however, the familiar cellular concept which would attribute the delay in appearance of the reaction to the supposed necessity for the skin cells first to become sensitized by fixation of the injected antibody.

More significant are the experiments demonstrating the presence of histamine and other physiologically active substances in the body fluids which are in contact with sensitized, reacting tissue cells. These humoral substances have been shown capable of causing typical contractions of *normal* smooth muscle tissue.

Alexander and associates[3] perfused the lungs of sensitized guinea pigs, then ground up the tissue and mixed this tissue emulsion with a measured amount of antigen. After centrifugation, the supernatant fluid was tested by Schultz-Dale method on one horn of the uterus from the same animal. To the other uterine horn was added the same amount of antigen alone. Fifty per cent of the animals showed a greater response of the uterine muscle to the antigen-tissue mixture than they did to the antigen alone. This exaggerated reaction indicated the presence in the fluid surrounding the sensitized lung tissue, after addition of antigen, of a smooth muscle-stimulating substance, evidently having an additive effect. These findings were confirmed by Ramsdell,[97] who incidentally mentions the irritating effect on smooth muscle of the guinea pigs' own serum. She concluded that tissue extracts alone are stimulating to smooth muscle, and that the specific reaction with antigen is augmented by a substance produced by antigen acting upon sensitized tissue, either by liberating more of the cell contents, or by forming a secondary reaction product.

In 1932, Dragstedt and Gebauer-Fuelnegg[46] demonstrated that in the majority of instances of severe or fatal anaphylactic shock in the dog, there appears for a few minutes only, in the vena caval blood and in the thoracic lymph, a smooth muscle-stimulating substance which the authors identified as histamine. Histamine in the blood of dogs and of guinea pigs during anaphylactic or peptone shock was again demonstrated by Tinel and co-workers,[113] Code,[28] and others. In the blood of sensitized rabbits in vitro, histamine is released from the blood cells into the plasma on addition of antigen.[45, 68] Platelets may be the principal source of the histamine in rabbits.[29] Peptone will release histamine into the plasma in *normal* rabbit blood[115] and so also will incubated mixtures of human serum (from untreated allergic patients) and the specific allergen.[109] Recently Noah and Brand[85] have reported the detection of an average increase of 900 per cent in the amount of plasma histamine in ragweed-sensitive patients when the heparinized fresh whole blood was incubated briefly with ragweed antigen.

In 1932 Bartosch and collaborators[5] perfused the isolated lungs of sensi-

tized guinea pigs with Tyrode solution to which antigen was added and found that a histamine-like substance appeared in the perfusate. Similar findings were reported by Daly and associates[40] and by Schild.[103] Especially significant would appear to be the observations[6] on the anaphylactogenic effect of the "shock fluid" collected from the lung veins of the animals. This fluid produced a marked reaction, typical of anaphylaxis, in normal guinea pig lungs. Similarly, Ungar and Parrot[117] demonstrated that the addition of antigen to a bath containing sensitized lung tissue *and* a strip of normal guinea pig intestine caused a marked contraction of the latter.

Of further interest in this connection is the work of Kulka.[74, 75] This investigator observed typical contractions in *normal* guinea pig uterine strips when antigen and antibody were made to combine in the fluid surrounding the tissue. A state of refractoriness developed after repeated exposure to the antigen-antibody mixture. In further experiments, using rabbit antipneumococcus serum and specific polysaccharide hapten, it was found that contractions of the normal smooth muscle were regularly obtained if the mixture also contained a small amount of fresh normal guinea pig serum. The phenomenon was shown to be dependent upon the presence of free antibodies in the fluid. These provocative studies need to be repeated and extended, but as they stand they appear to offer evidence for a purely humoral origin of a muscle-stimulating (anaphylactogenic) substance.

Campbell and Nicoll[25] reported the explosive appearance of a material in the tissue fluid around sensitized guinea pig lungs, after addition of antigen, which produced a sharp contraction of normal *rat* uterus, suspended in the same bath. Since the rat smooth muscle is refractory to ordinary doses of histamine, this is one of the evidences, as mentioned previously, for the nonidentity of the active substance with histamine.

That physiologically active materials other than histamine are released in the body fluids in anaphylaxis is now well established. Kellaway and Trethewie[71] first showed the presence during reactions of a "slow reacting muscle-stimulating substance." This new principle has been named bradykinin.[11, 101] Heparin, released during anaphylactic or anaphylactoid shock, is presumed to be responsible for the loss of normal coagulability of the blood.[105] Still other biologically significant reaction products undoubtedly form.

The presence of these active substances in the body fluids surrounding reacting tissues has for the most part been interpreted[37, 44] as further evidence for the cellular-histamine theory, and not as supporting a humoral-anaphylatoxin concept, especially since their release (at least in small amounts) has repeatedly been demonstrated in isolated tissues, perfused free of blood.

The recent studies of Rocha e Silva and colleagues, however, have revealed that the blood is not entirely passive, if included in such experiments, and also it has been shown that anaphylatoxins are potent agents for the release of histamine-like substances. Rocha e Silva noted that in the experiments of Bartosch and associates[5] and of other investigators, in which

the isolated, sensitized guinea pig lungs, or the liver of dogs, were perfused with Tyrode solution to which antigen or peptone was added, the perfusion fluid was found to contain only small amounts of histamine, measurable in micrograms. But when he repeated the dog liver perfusion experiments using whole, unclotted blood in silicone vessels, plus peptone or antigen, far greater amounts of histamine were liberated (e.g., 8 mg.), as well as not less than 25 mg. of heparin.[100] Thus the presence of whole fresh blood was shown to contribute materially to the result.

Later Rocha e Silva, with Aronson and Bier, showed that an anaphylatoxin prepared by treating homologous (guinea pig) serum with agar, when perfused through the isolated lung tissue of a normal guinea pig, caused the immediate appearance of considerable amounts of histamine (e.g., about 30 μg) in the perfusate, more appearing in the next few minutes. An anaphylatoxin similarly prepared from rat serum was even more potent. Moreover, rat serum anaphylatoxin was found capable of causing regularly a contraction of the normal guinea pig ileum. This reaction was apparently mediated by release of histamine, since it was blocked by antihistaminics.[100, 102]

Further evidence indicating more than a passive role for humoral factors is presented in the work of Humphrey and Jaques.[82] In studying the release of histamine into rabbit plasma by antigen-antibody reactions in vitro, they found that purified antigen-antibody systems did not cause histamine release unless fresh, unheated plasma was present. The rate of release increased with increasing amounts of plasma in the test system. Another interesting observation was made when plasma in which antigen-antibody reactions had occurred was injected intradermally into rabbits that had previously received an intravenous inoculation of a blue dye. An immediate skin reaction, varying in diameter of the blue area with the histamine content of the injected material, was observed, but, in addition, an entirely distinct, more intense bluing developed somewhat more slowly, reaching a maximum in about twenty minutes. This latter reaction, clearly different from that caused by the histamine and evidently a result of the preceding antigen-antibody combination in the specimen, could only be attributed to "a lasting change in the plasma itself."

CONCLUSIONS

It thus appears that the validity of the idea of a humoral source for at least some of the factors responsible for hypersensitivity reactions, as opposed to an exclusively cellular sensitization and injury, can now be reasserted with some confidence. Realization that both humoral and cellular factors contribute significantly to the chain of events that follows antigen-antibody union in the sensitized host should help to reconcile the opposing theories. Fundamental questions remain, however. Neither theory offers a fully satisfactory explanation for the intimate mechanism of the primary injury, or for the basic conditions which determine the existence of a hypersensitive state as contrasted with a desensitized state. Perhaps important answers will be forthcoming through current studies on the possible role of plasma and tissue proteases

(Ungar,[116] Humphrey and Jaques,[62] and others). Discussion of this intricate problem is beyond the scope of this review.

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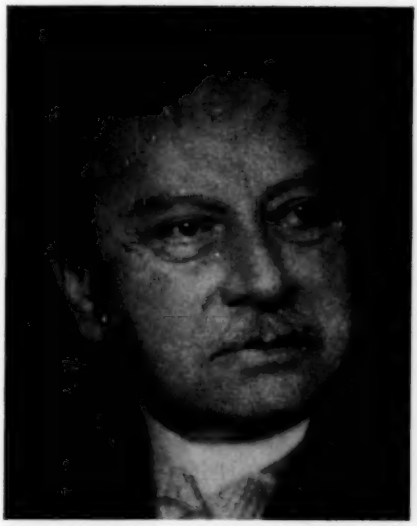
Pediatric Profiles

Adalbert Czerny

(1863–1941)



ADALBERT Czerny was born on March 25, 1863, in old Austria. He studied medicine at the University of Prague which, at that time, had an excellent reputation; its medical faculty consisted not only of outstanding scientists and teachers but of great personalities who had a strong influence on the students. Czerny's main interest was physiology. While still a student, he began his investigations on the primitive kidney under the supervision of Prof. S. Meyer, who, recognizing the ability of his young pupil, made him assistant at the physiological institute while Czerny was still a student. Later on Czerny worked with the renowned physiological chemists Huppert and Hofmeister.

Having acquired a good training in histology, embryology, and physiological chemistry, Czerny wanted to do internal medicine but could not find an opening at the University Hospital. Thus he accepted an assistantship with Prof. A. Epstein at the "Findelanstalt" (foundling institution) in Prague, affiliated with the University and used as a teaching institution for pediatrics. The Findelanstalt admitted healthy newborn infants who spent their entire infancy there; but, since it was a teaching institution, it included departments for sick infants and for young children. The rich material of the Findelanstalt offered rare opportunities for studying the physiology and pathology of the infant. It was lucky for pediatrics that Czerny was given this position because here, owing to his keen powers of observation, he conceived many ideas which proved extremely fruitful in pediatric research later.

Czerny's influence on modern pediatrics was unique. I shall briefly mention the problems that occupied

him and his school. In order to evaluate his work, one has to consider the state of pediatrics of about sixty years ago. At that time it was a real risk to feed an infant artificially, since morbidity and mortality of infants fed on cow's milk were extremely high. Whenever possible, infants were breast fed. The problem was to find the noxious principle in cow's milk. Some investigators incriminated cow's milk casein. The milk hygiene was, of course, very poor. Infants were fed without schedule; mothers considered crying a sure sign of hunger, as unfortunately they still frequently do today, so that infants were fed and often overfed with a poor quality milk, which, in addition, was not hygienically prepared. Every summer brought with it a high mortality due to diarrhea. The artificially fed infants who survived reached the winter months in a malnourished state and then many succumbed to pneumonia. At that time medical thinking was concerned with organ and cellular pathology and bacteriology. Such were the conditions when Czerny entered pediatrics.

His first work in Prague dealt with colostrum and led to the clarification of the nature of colostrum corpuscles. Soon his attention turned to problems of nutrition. He proposed that infants be fed at the breast not more often than every three hours, artificially not more than every four hours. Such proposals, revolutionary at that time, were the results of observing the normal emptying times and the stomach chemistry of numerous healthy infants, some fed with human milk and some with cow's milk. That time marks the origin of investigations on infectious and noninfectious gastrointestinal disturbances of the infant, on normal and abnormal respiration, and on sleep in childhood. Czerny's publications soon attracted some attention and when, in 1894, the universities of Innsbruck and Breslau both offered him a professorship, he chose the University of Breslau.

Many physicians from Germany as well as from abroad came to join him in his work in Breslau. This marked the beginning of the "Breslau school," which produced a number of outstanding pediatricians. In Breslau a new approach to the formerly so-called gastrointestinal diseases was begun; the concept of nutritional disturbances was created, and nutritional disturbances etiologically classified. This, in turn, opened new therapeutic possibilities. Czerny recognized early that weight gain alone is no indication of proper feeding. He defined as the aim of proper feeding not only satisfactory physical thriving, but also the development of an optimal resistence. He introduced the concept of "turgor" into pediatrics, stressing the fact that tissue turgor is an important sign for judging the nutritional status of an infant. He pointed to the meaning of colloidal water retention and recognized that the marked fluctuations of body weight in the sick infant are based essentially on fluctuations in the water and mineral contents of the body.

Contrary to the then prevailing anatomically oriented organ pathology, Czerny stressed (1895) the functional entity of the human organism. This concept of functional entity remained a guiding principle in all his investigations. Already in Breslau Czerny was

struck by the fact that children responded differently to the same disease and identical treatments. These observations led to the re-evaluation of the notion of constitution, and finally to the concept of the "exsudative diathesis." The constitutional approach, in turn, led Czerny to the question of heredity and of the differences in the functional make-up of the central nervous systems of children. These problems interested him throughout his life. In 1901, Czerny published his observations under the title "Children of Neuropathic Parents." Clinical observation and considerations of constitutional pathology caused Czerny to reject the then prevalent notion that scrofulosis was a disease entity; instead he showed that scrofulosis was identical with tuberculosis and that the manifestations thought to be characteristic of scrofulosis were due only to the reactions of an abnormal constitution to the combination of tuberculosis and faulty nutrition and secondary infection. Later years proved the validity of Czerny's interpretation, for, as modern principles of infant feeding and hygiene came into use, scrofulosis disappeared, whereas tuberculosis persisted.

Intensive studies were devoted in Breslau to the metabolism and the chemical composition of the body in infancy. Malt soup was introduced into infant feeding, which was a step forward in dietetic treatment at the time. The occurrence of acidosis in severe acute diarrheic conditions was demonstrated. Paravertebral pneumonia was described and the cathodal hyperirritability in infantile tetany was observed. Anatomical studies on the thymus gland were carried out with a remarkable result. It could be demonstrated, contrary to the general opinion, that respiratory difficulties as occasionally noticed in infants can never be caused by a primary compression of the trachea through the enlarged thymus. The truth of this observation is being recognized only recently.

When Czerny accepted the chair of pediatrics in Breslau, there was no children's hospital; this was founded later. In the beginning a rented villa which could accommodate sixteen children served as the children's hospital. There outpatients were also seen, and scientific work was carried out in a small laboratory. Space was so scarce in the laboratory that the work had to be done in two shifts, one at daytime, one during the night. Such were the modest circumstances under which the foundations of modern pediatrics were laid. Czerny spent almost all day in the hospital and even returned after supper to supervise his pupils' work in the laboratory and to discuss with them his scientific ideas. Even when newly wed, he did not change this routine, much to the chagrin of young Mrs. Czerny who told me how many nights she spent weeping and how long it took her to reconcile herself to her husband's ways.

Czerny remained in Breslau for sixteen years. In 1910 he accepted an appointment as Professor in Strassburg, where he took over the then new, most modern children's hospital in Germany. He was happy to rejoin here his old teacher Hofmeister, and also the famous internist and cardiologist Wenkebach who became his lifelong friend. Research was continued

in Strassburg and this period also had its highlights. Problems of nutrition were studied further; the fermentation of simple and complex carbohydrates by intestinal bacteria was analyzed and the role of various cereals in infant nutrition was studied. Czerny was interested in the interaction of natural immunity and nutrition and already then pointed to the importance of vitamins. He stressed the fact that cow's milk does not contain a sufficient amount of vitamins to cover the needs of the infant. In a monograph still worth reading today, he deals with the question of starvation. In Strassburg investigations dealing with conditioned reflexes and their bearing upon pediatric problems were initiated. Czerny continued his studies of the constitutional differences between the nervous systems of children, and wrote on the "Sensitive Child." During the Strassburg period, the greatest sensation was caused by Czerny's description of alimentary anemia, on which he reported at the first International Congress of Pediatrics, in Paris in 1912. His paper was received with more doubts than understanding; the time was not ripe for the idea. Today the concept of alimentary anemia is universally accepted and even self-evident in pediatrics. I am sure there are only a few pediatricians today who realize that Czerny was the originator.

When Czerny published his paper on exsudative diathesis, French pediatricians considered it to be the same as their "arthritisme" and that there was nothing new about it. If the French are right then, Czerny reasoned, a diet rich in purines ought to produce symptoms of exsudative diathesis; he therefore added liver and thymus to the infants' food for prolonged periods. So far as exsudative diathesis was concerned, this experiment had negative results, but Czerny made the interesting observation that after the infants had been fed with liver for some time, they developed unusually good color and showed remarkably high hemoglobin levels and erythrocyte counts. On the basis of these observations, he recommended the use of liver in the dietetic treatment of alimentary anemia; we always used this treatment in Czerny's clinic.

Czerny's lectures delivered in Breslau were published in a small volume under the title *The Physician as Educator of the Child*. In these lectures he discusses, in easily understandable words, problems of child psychology and pedagogy. This little book met with great success. It was translated into many languages and republished many times. The well-known Russian pediatrician Rauchfuss once said that this was Czerny's best opus.

In 1913 Czerny took over the children's hospital of the Berlin University. In spite of the limitations imposed by the World War I and the postwar period, work in the clinic progressed. Problems of nutrition and nutritional disturbances, together with questions of metabolism and constitutional pathology, continue to be the main interest. Czerny published a paper on difficult children; furthermore he was interested in finding out what is congenital and what is acquired in children. As a result of food scarcity during the war the butter-flour mixture was recommended and as early as 1919 it was shown, by metabolic experiments, that young infants are well

able to digest meat. Through many years experimental investigations on acute intestinal disturbances and dehydration were carried out and it could be demonstrated that the alimentary intoxication of infants is not an etiological entity, but is due to a circulatory shock brought on by various possible causes. Chloride acidosis in severe diarrhea was described for the first time; purpuric diseases were studied with a new approach and classified in a new way. Epituberculosis was described, though its clinical significance is still not understood. It was in the Berlin Clinic that the diagnosis of Niemann-Pick disease was made for the first time in vivo by puncture of the spleen. The description of Niemann-Pick disease came also from the Berlin Clinic. Investigations on reflex phenomena of premature infants were carried out and published. In 1925-1926, the second edition of Czerny-Keller's "Handbuch"* appeared, an outstanding pediatric text.

I have mentioned only some of Czerny's work here in order to show how essential a role he played in shaping modern pediatrics. Many of his ideas and observations became common knowledge to physicians still during Czerny's lifetime; some became so self-evident that their author himself fell into oblivion.

In a popular article Wilhelm Ostwald, one of the founders of modern physical chemistry, divided scientific men into two groups, the classics and the romantics. According to Ostwald's definition Czerny represents the romantic type. He disliked being alone. His contact with patients enabled him to observe medical phenomena and his contact with colleagues and students further stimulated his ideas. Such stimuli were a necessity for Czerny; this is surely why he would never have thought of missing his clinical lecture and the ensuing rounds. One morning the adjutant of the Kaiser came to fetch him to see the crown prince's sick child. Czerny refused to leave the clinic on the grounds that he had to deliver his lecture and he had to make rounds first; this refusal did not make him popular at the imperial court. During a scientific discussion, Czerny would forget time and space, and all too often Mrs. Czerny, expecting him for dinner, would be kept waiting for hours.

In spite of his poise, Czerny was a sensitive, impulsive, and moody man. He was usually ill at ease and irritable before his lecture which was scheduled to start at noon. He never prepared it, but at 11 A.M. his lecture assistant would come up to propose cases suitable for the lecture, which could then actually be produced among the patients of the hospital. This was a most disagreeable task because it was extremely difficult to satisfy Czerny. At the beginning of a lecture, he always wanted to present patients with symptoms recognizable from a distance, for instance, a typical purpura, or hydrocephalus, or a whooping cough spell, etc. Since there were so many patients in the hospital, such requests could usually be satisfied; but things became difficult when the main topic for the lecture had still to be decided on and when, without even listening to the proposals, Czerny would suddenly request a typical funnel chest,

*Des Kindes Ernährung, Ernährungsstörungen und Ernährungstherapie, F. Deuticke.

or a very pale child without anemia, or a blue baby, or a lingua geographica, etc. He never looked for diseases, but always for a salient symptom. These prelecture difficulties irritated Czerny. But as soon as he entered the auditorium he forgot his anger and, proceeding from one symptom, he would then discuss the physiology and pathology with all ramifications and end up with a rounded picture of the whole entity. These lectures, always improvised, were lucid, simple in style, and strictly logical in composition. They were original and stimulating and little of what one would hear from him could be found in standard textbooks. In spite of his simple style, Czerny presumed quite a bit of knowledge in diagnostic and pathological physiology on the part of his listeners. A certain degree of disciplined thinking was requisite to follow him.

The question whether Czerny was a suitable teacher for students is debatable. The answer depends on the aim the professor pursues in teaching. If his main goal is to acquaint the students with the elements of diagnosis and treatment, then Czerny was a poor teacher; but if his goal is to inspire the talented students, to fill them with enthusiasm and stimulate them with his ideas, then there were certainly very few professors who could be his match. To understand this correctly, it must be mentioned that the German academic teacher was not primarily a teacher of standard knowledge and techniques; he was a man who espoused and professed the cause of science, enjoying full academic freedom to express his scientific convictions.

The lectures were supposed to end at 1 o'clock, but never did, although the big electric clock of the auditorium hung directly opposite Czerny's eyes. He would only stop after bringing his thoughts to a certain conclusion. Immediately after the lecture Czerny, being an ardent smoker, would light a cigar. After a short pause in the anteroom he started his clinical rounds which were held also in the auditorium because it was impossible to take such a great number of staff physicians and guests through the wards. Every day another department presented its patients. The children entered fully undressed and Czerny often examined them himself. After that he would ask questions, relate his own experiences, make suggestions to clarify difficult cases or inspire ideas for new therapeutic or scientific research. Everyone was welcome to take part in the discussions at these rounds. As mentioned before, time never mattered for Czerny, and when he was interested in a problem he did not care if the time alloted for the rounds was long overstepped.

It was a hard task to convince Czerny. If one would tell him, for instance, about a new observation at the bedside or praise a new treatment, his stereotype answer was "zeigen" which means "let me see it." On the other hand, he frequently reminded us never to deny something only because one had not yet seen it. New therapeutic proposals, if they seemed sound and promising, had to be tested. He was happy if they proved to be fruitful, because he enjoyed each step forward in pediatrics, no matter how small. However, if an alleged observa-

tion could not be verified, Czerny had no use for it, no matter whence it came.

Research work carried out in the clinic had to be presented to Czerny before publication. He read all the papers and discussed them with the author. He insisted that all relevant references be included and that all quotations be exact. He would return a paper if the references were incomplete.

I worked with Czerny for about twenty years, and was again and again surprised by his powers of observation and his scientific intuition. Occasionally our opinions about certain subjects differed, and I sometimes thought he was wrong. Sooner or later, however, I had to admit that in such cases Czerny, and not I, had been right.

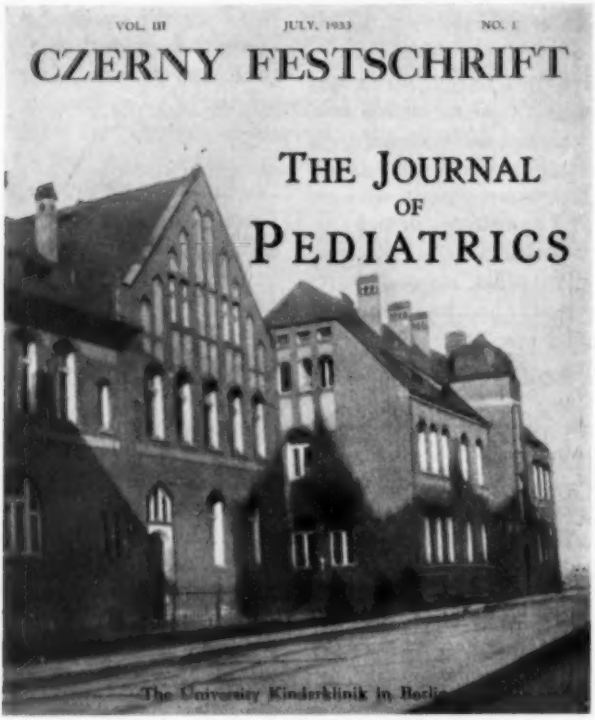
His great charm, his straightforward and plain nature made it easy for Czerny to win the people with whom he came in contact. However, since he always had the courage to stand up for his convictions and since he never would compromise, it was only natural that some of his criticisms were resented and that he made enemies. As a young assistant of the Findelanstalt in Prague he once visited the children's hospital in Leipzig, then under Prof. Heubner's direction. Heubner demonstrated to Czerny a new method of checking cow's milk before feeding it to infants and considered it as a great advance in the artificial feeding of babies. Czerny, however, noticed that many of the infants fed with Heubner's checked milk died nevertheless. During some of the rounds, he told Heubner that infant mortality in the hospital in Prague was considerably lower, though Heubner's method of milk control was not used. Heubner resented this remark very much and never forgot it. Even Heubner's assistants from that day on refused to speak to Czerny. He therefore returned to Prague with the feeling that he had made only enemies in Leipzig. It is to Heubner's credit, however, that shortly after this incident he recommended Czerny to the Prussian minister of education for the professorship in Breslau. Czerny found this out thirty years later to his great surprise when he read Heubner's autobiography which then appeared.

Being a highly sensitive person, Czerny not infrequently displayed sudden changes of disposition. When in a bad mood he was very negative and occasionally even unjust; but a bad temper never lasted long with him, and as soon as it passed he did everything to correct the injustice.

Czerny took little interest in everyday problems, nor did he care about money. He did not take private patients for treatment and refused to establish a department for private patients in his hospital. He had office hours four times a week but did not accept more than four patients a day. He disliked a consultation practice and often refused to go, especially if he happened to be listening to a good concert.

He was not interested in politics. When the Nazis came to power he was already professor emeritus. Unexpectedly he was asked by the minister of education whether he would agree to take over the directorship of the University Children's Hospital in Düsseldorf temporarily. Czerny's old friend, Prof. Kraus, when asked for

advice, told Czerny he should accept if he thought he was in sufficiently good health for such a task. On two occasions he discussed the question with me. Since Czerny was in good health and at the peak of his mental alertness, and since I had frequently noticed, after he became emeritus, how much he missed the hospital and the



discussions with his pupils, I also advised him to accept the chair. He then agreed under the condition, however, that he would be free of any obligations except clinical work and teaching. This was granted and Czerny left for Düsseldorf where he remained for two years. Certain people blamed him for having accepted this appointment and even suspected him of sympathizing with the Nazi regime. Such a surmise was, of course, absurd; he was a man without any prejudices and he hated nothing more than brutality and coercion. He was certainly a good German and clearly foresaw the dangerous menace to Germany of the new regime. I have a vivid recollection of an evening when he visited me, obviously excited. When I asked him for the reason, Czerny told me the following: While reading in his study that afternoon, he suddenly heard his wife crying in the next room. Alarmed, he went in, found her at the window, pointing to uniformed Nazi youths marching

past their house and screaming the "Horst Wessel Lied." Czerny and his wife then asked themselves, "Is this what has become of our Germany?" This happened in the beginning of the Nazi regime. During this time Czerny used to speak to me often over the telephone and frequently criticized the regime with such words that I had to hang up the receiver in Czerny's and my own interest. I knew from my own experience that telephone conversations were being overheard at that time.

Czerny was a benevolent man with kind understanding for minor human weaknesses. He was a generous giver. Many a work which he inspired and directed he let his assistants publish without putting his name on the paper, not even if he had left his own observations and thoughts at their disposal.

He was an artistically highly gifted person. He was a good painter, an excellent violinist and a great lover of music. Up to his old age he had regular chamber music evenings in his beautiful home, where he played the violin, his son the cello, and professional musicians participated. He loved life and knew how to enjoy it. With great tenderness he was devoted to his only, very talented, son. He was happy and grateful to see him married and very pleased when he was appointed professor of physics at the University of Frankfurt a. M. His three grandchildren were his great pride. His marriage with Mrs. Czerny was a very harmonious one. Mrs. Czerny was an ideal wife to Czerny, with the admirable ability of managing all the little daily events which did not interest her husband without bothering him. Science and music were his domain, all else fell into her realm.

The death of this great man was just as unpretentious as his life had been. He died on October 3, 1941, at the age of 78. It was his wish to be buried in the family vault in Pilsen.

Erwin Schiff

Comments on Current Literature

PHYSIOLOGIC CONTROL OF RED CELL PRODUCTION

RECENT investigations in the field of hematology are re-emphasizing the dynamic character of the relationship between the blood and its organs of formation and destruction. An excellent critique of present-day knowledge concerning this dynamic relationship has been prepared by Allan J. Erslev[1] of the Murphy Army Hospital, and appears in the September, 1955, issue of *Blood* under the title "Physiologic Control of Red Cell Production."

Basically the formation of red cells requires the presence of healthy primordial elements in the bone marrow. Under ordinary circumstances, their production is stimulated by reduced oxygen content of the blood, a condition which may accompany hemorrhage, hemolysis, cardiac or pulmonary disease, etc., or simply be associated with breathing in an atmosphere low in oxygen content. If the necessary elements for blood cell production are available in adequate amounts, a condition of chronic anoxia will lead to polycythemia. The manner in which anoxia serves as a stimulus to erythropoiesis has not been explained adequately. The useful and relatively simple concept of tissue anoxia in the bone marrow itself, as the essential control mechanism for erythropoiesis, has not been substantiated by direct measurements of oxygen tension of bone marrow in acute and chronic anemia, nor by in vitro studies of bone marrow activity. That some humoral factors might play a significant role in erythropoiesis was suggested early, but not verified; likewise, early animal studies suggested that animals rendered anemic experimentally have in their blood some element which on transfer enhances blood production in normal animals. However, convincing experimental evidence for the existence of such an erythropoietic factor, or factors, has been provided only very recently. Erslev summarizes the significant findings during the past few years with respect to: basic requirements of erythropoiesis, regulation of erythropoiesis, tissue oxygen tension, and erythropoietic factors, including some reference to his own investigative work and that of his associates.

Basic Requirements.—While certain basic metabolic elements are necessary for satisfactory mitosis and proper maturation of the immature erythropoietic cells, these elements do not, according to the more recent interpretation of the process, enter into the physiologic control of red cell production. Significant dietary factors and endocrine factors have been well delineated. "A deficiency in any of these components of the metabolic environment" may "result in a decrease in the production of normal hemoglobin because of impaired erythroblastic maturation and/or suboptimal rate of multiplication."[1] When the basic requirements, nutritional, hormonal, etc., have been met, red cell production proceeds in a normal fashion, each red cell containing a specific amount of hemoglobin.

Regulation.—As the author indicates, regulation of red cell production is apparently not dependent upon a simple relationship such as oxygen demand, or alterations in tissue tension of oxygen. "The degree of tissue

oxygenation, or the tissue tension of oxygen, appears to regulate the production of mature red cells through changes in the rate of erythroblastic multiplication, rather than through changes in the speed of cellular maturation.''[1] Cellular maturation with synthesis of hemoglobin seems to be a process which under normal circumstances is essentially self-limited, and not significantly influenced by demands for an increased or decreased red cell production. Specific humoral components have been suggested as more plausible regulatory factors in the speed of maturation of red cells, and in their release from the bone marrow. Normoblastic multiplication, on the other hand, Erslev states, has been shown to respond rapidly to demands for an increase or decrease in red cell production. Within one hour of the demand, there is observable change in the number of normoblastic mitoses. However, because of fixed speed of cellular maturation, a significant change in red cell count cannot be expected for several days following demand. When there is prolonged or intense demand for red cells, mitoses begin to appear in dormant multipotential reticulum cells of the yellow bone marrow, the spleen, and the liver, and these cells will develop into normal erythrocytes. This process is activated slowly and is probably not too significant in acute demands, but once activated, the process does allow for many-fold increase in red blood cells.

A regulatory mechanism, dependent upon tissue tension of oxygen alone, would call for changes in oxygen tension in some specific cellular system. High-altitude studies[2] have suggested that even if the immediate effect of lowered tissue tension is a compensatory increase in mitotic activity of erythropoietic tissue, there would be a lag in red cell increase due to the fixed speed of intramedullary maturation of immature red cells. Under circumstances of acclimatization to high altitude, induced compensatory adjustments may occur in the pulmonary and cardiovascular functions.[2] These adjustments do not restore the tissue tension in the erythropoietic center to normal; were they to do so, the anoxic stimulus to red cell increase would not occur. Continued stimulation of red cell production, despite compensatory pulmonary and cardiovascular adjustments, suggests that these adjustments are incomplete or of short duration. From a study of erythropoiesis in experimental dilution anemia, Erslev[3] suggests that the erythropoietic center may be "located in an organ from which, during tissue anoxia, blood is shunted to vital oxygen sensitive tissues. This local diversion of blood away from the erythropoietic center would maintain a reduced oxygen tension in the center until final adjustment is accomplished by an increase in red cell volume."[1]

Erythropoietic Factors.—Evidence for the presence under certain circumstances of an erythropoietic factor, or factors, in blood plasma or serum has accumulated from investigative and clinical observations, particularly from experimental attempts to increase red cell production in normal animals by the administration of blood plasma or serum from animals rendered anemic experimentally. For various reasons, these observations and experimental results have been difficult to evaluate. Of necessity the quantity of serum administered was small. In 1953 Erslev[4] reported that under controlled conditions larger quantities of plasma could be used (17 ml. per kilogram, once a day for four days, plasma from anemic rabbits to normal), and that on this regime the recipients showed clear-cut, reproducible reticulocytosis. This reticulocytosis was associated with a normoblastic hyperplasia of the bone marrow, indicating that a true stimulation of erythropoietic function had been induced by the plasma administered. Normal plasma, on the other hand, administered in like amount did

not influence erythropoietic function. Continued administration of plasma from anemic to normal rabbits (thirteen infusions of 17 ml. per kilogram in a period of eighteen days) resulted in significant polycythemia. Similar results in monkeys were less striking, but of significant level.[5] Myelopoietic and thrombocytopoietic functions are apparently not influenced, since white blood cell and platelet concentrations remained unchanged. Unexpected support for the significance of an erythropoietic factor has come from clinical observations of patients with polycythemia secondary to a retrograde flow of blood through a patent ductus arteriosus.[6] Such patients show a normoblastic hyperplasia of bone marrow in the part of the body which was supplied with blood containing a normal amount of oxygen. The explanation considered most logical for this finding is that of stimulation by an erythropoietic factor released somewhere in the hypoxic part of the body. A similar explanation has been given for fetal polycythemia in infants born of anemic mothers, suggesting a placental transfer of an erythropoietic factor.[7] The biochemical nature of the erythropoietic factor is being studied currently by a number of investigators. Erslev and Lavietes[8] have been able to show that the factor is present in serum as well as in plasma, that it is not dialyzable through a cellophane membrane, and that it is present in the fraction of serum which contains albumin, alpha globulin, and beta globulin. These findings, which are reproducible, would indicate that the erythropoietic factor is essentially protein in nature.

In a summary conclusion, Erslev proposes "as a working hypothesis, that the function of erythropoietic tissue is controlled at least in part by the blood level of a humoral erythropoietic factor, . . . this factor . . . most likely produced in a specific, extramedullary organ or tissue system where its rate of production is regulated by the tissue tension of oxygen."[1]

The author states that additional studies are needed in order to confirm or modify this hypothesis, but that "it forms a useful basis for future research into the dynamics of red cell production in normals and in patients with blood dyscrasias."[1]

RUSSELL J. BLATTNER

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News and Notes

Dr. Robert E. Cooke, associate professor of pediatrics and physiology at Yale, has been appointed professor of pediatrics and head of the department at Johns Hopkins Medical School. The appointment is effective in June of this year.

Dr. Hilda Knobloch, formerly assistant professor in the Division of Maternal and Child Health of the Johns Hopkins University, School of Hygiene and Public Health, has been appointed to the staff of the Children's Hospital, Columbus, Ohio, as associate professor of pediatrics at the Ohio State University College of Medicine.

The **Harvard University School of Public Health** announces public health scholarships for the academic year 1956-1957 will be granted to individuals of high professional promise in awards ranging from part tuition to tuition plus a stipend, according to the qualifications and financial needs of the applicants. The scholarship funds are primarily intended for citizens of the United States. In general, preference will be given to applicants under 35 years of age. Scholarship applicants must be eligible for admission to the School as a candidate for one of the following degrees: Master of Public Health, Doctor of Public Health, Master of Science in Hygiene, Doctor of Science in Hygiene, Master of Industrial Health. Scholarship applicants must return completed admission and scholarship applications to the Harvard School of Public Health by March 1, 1956. Scholarship awards will be announced May 1, 1956. Under exceptional circumstances awards will be made at other times.

The fifth annual postgraduate seminar for pediatricians will be conducted at **St. Christopher's Hospital for Children**, Philadelphia, by the Department of Pediatrics of Temple University School of Medicine from May 16 to 19, inclusive. Sessions will be devoted to problems in the fields of pediatric hematology, cardiology, surgery, endocrinology, psychiatry, neurology, infectious diseases, pathology, etc. For information regarding enrollment, registration fee, etc., write to Dr. John B. Bartram, St. Christopher's Hospital for Children, 2600 North Lawrence St., Philadelphia 33, Pa.

Applications for the *residency* from Jan. 1 to Dec. 31, 1957, in Pediatric Oncology at **Memorial Center for Cancer and Allied Diseases** in New York will be received up to April 15, 1956. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary: $3,600 annually plus maintenance. For application forms and information write: Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 East 68th St., New York 21, N. Y.

Merrill-Palmer School announces a new graduate and postgraduate program of intensive research training in human development and family life. One-year programs designed to supplement graduate training in psychology, sociology, education, and home economics will offer students supervised research experience in an ongoing project or in one initiated by the student. The direct research activity, comprising over one-half of the student's time, will be combined with course work including an advanced seminar on the role of theory and method in research in human development and family life and elective course. Fellowships are available with stipends from $1,000 to $2,500. Application will be acted on beginning

March 1. For further details write to: Dr. Irving Sigel, Merrill-Palmer School, 71 E. Ferry Ave., Detroit 2, Mich. For information on fellowships write to the Registrar at the same address.

The **Massachusetts Advisory Committee on Polio Vaccine** at its meeting on Jan. 9, 1956, has voted to advise the Massachusetts Department of Public Health to resume the mass polio vaccination of school children. This decision arises from evidence that the more recently produced vaccine has a sufficiently greater level of safety than that previously available to warrant its use. The Committee believes that the protection to be expected is now greater than a potential risk to the vaccinated individual and to those with whom he comes in contact.

However, the Committee also believes that total freedom from live virus cannot be assured in this vaccine and that the vaccine may possibly, on rare instances, induce the disease in those vaccinated or in their contacts. Furthermore, it recognizes that the search still continues for a suitable substitute for the virulent Mahoney strain.

The Committee arrived at this decision on assurance from Washington that the vaccine now available to the State from the Federal Government would comply with the new methods of production and additional safety tests introduced by November, 1955, or the equivalent requirements established through the initiative of manufacturers of the vaccine prior to this date. All physicians are advised to administer polio vaccine made according to these latest specifications.

The Committee's action was influenced also by recognition that the interepidemic period is the safest time for vaccination.

The Committee finds there is no evidence that the vaccine caused the recent epidemic in Massachusetts.

In making this recommendation the Committee is aware that the present vaccine has not as yet undergone full field experience to determine the degree of its effectiveness although it has passed required laboratory potency tests. Furthermore, at the present time the ultimate duration of protection conferred by any polio vaccine is not known.

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In addition to the above specific recommendations made to the Commissioner of the Department of Public Health regarding the resumption of the polio vaccination program the Committee made the following comments:

Criticism has questioned the right of the Committee to rest its explanation of delay on "knowledge from authoritative sources" that live virus has been found in the vaccine prior to November, 1955. Scientists both in government and private manufacturing firms are often forbidden to divulge the results of their work. A firm making vaccine may find live virus in its product. The firm promptly condemns the entire batch of vaccine, but for very natural reasons affecting the sale of is product does not announce this to the world. Nevertheless, these scientists meeting in privacy discuss their difficulties, hoping for mutual help in their problems. There are members of the Committee who have received such confidential information. Such information is highly respected, as are confidences held by physicians, the clergy, and the legal profession.

Criticism has also been leveled at the Committee for allegedly distinguishing between its advice to the Department of Public Health regarding the free vaccination of school children and the advice to private physicians regarding the vaccine. There has never been any difference in the advice of the Committee in these two respects. The Committee has advised the Commissioner of Public Health and the Public Health Council, and through these all public health units in the state. The Commissioner and the Council have followed the advice of the Advisory Committee, and the free vaccination of school children was deferred. Many practicing physicians did not agree with the recommendations of the Advisory Committee, and, being free to give the vaccine, have been doing so.

There is an element of danger in the administration of all vaccines. For the most part, such danger consists of unusual reaction on the part of the individual. The possible inherent dangers in the poliomyelitis vaccine have been reduced by concerted efforts on the part of the United States Public Health

Service, private manufacturers, and many other scientists working in this field, though the actual degree of improvement of safety has not been determined by field experience. Moreover, what effect such recent improvements toward the safety of the vaccine has on the efficacy of the material as a preventive of the disease is yet to be determined. Indeed, the vaccine is very definitely in the developmental stage and needs much more scientific study. One cannot expect perfection at this early date. For this reason the Committee has been confronted with great difficulties. Vaccines for the prevention of other diseases have undergone radical improvements over a period of years, and the same is to be expected in the field of poliomyelitis.

Books

An Introduction to Psychiatry. Max Valentine, M.D., D.P.M., Baltimore, 1955, Williams and Wilkins Co., Price $3.75.

Present-day psychiatry with its many schools of thought may be described as somewhat of a bedlam. To the confused medical practitioners (probably 100 per cent) and to the confused psychiatrists (at least 90 per cent), this small book by Dr. Valentine of the department of mental health of the University of Aberdeen can be heartily recommended. In straightforward language, unobscured by the jargon which makes about 99 per cent of the writing in the field of psychiatry obfuscated and esoteric, the author has succeeded very well in his aim of providing "a fairly concise background of factual information." The pediatrician will not only find the excellent chapter on "Child Psychiatry" of interest, but the remaining chapters which give him a good understanding of the fundamentals of psychiatry which is the current vogue in medicine.

Les explorations biologiques en pédiatrie. Claude Polonovski and Jean Colin, Paris, 1955, Expansion Scientifique Française, 500 pages. Price 3,900 fr. (French).

A manual of microchemical methods and techniques for use in pediatric clinics. The first part contains detailed methods for the blood, cerebrospinal fluid, urine, and feces. A second part discusses the methods of study of the electrolyte equilibrium, and methods of use for a particular organ or system, as the kidney, liver, etc. It is a very complete manual. For the blood alone some forty different tests are described. The authors show a wide familiarity with the biochemical tests worked out in many countries. In pediatric practice only small quantities of blood are usually available for study, and microchemical methods are a necessity. The text will be most useful for pediatric laboratories. The various discussions are concise and clear.

Biologische Daten für den Kinderartz, ed. 2. Edited by Joachim Brock, Berlin, 1954, Springer-Verlag, 2 volumes, 1834 pages. Price DM 198.

The first edition of Brock's biologic data for the pediatrician was published in 1932. Since that time a great mass of new material has been developed. In this new two-volume edition Professor Brock of Hamburg has called upon some twenty-five of his colleagues to write the individual sections. The text is a valuable work of reference containing basic biologic data. The first volume contains data on growth, the skeletal system, blood circulation, respiration, and nutrition; the second, data on metabolism, body fluids, internal secretions, cerebrospinal fluid, electroencephalography, etc. Most of the sections show a wide

knowledge of the work in the various fields that has been done in other countries. The bibliography following each section is, as a rule, excellent. The text will be of great value to research workers in the many fields which make up the total picture of modern pediatrics.

Year Book of Pediatrics 1955-1956. Edited by Sydney S. Gellis, M.D., Chicago, 1955, Year Book Publishers, 431 pages.

The current volume contains abstracts of articles appearing in journals from June, 1954, through May, 1955. The selection is representative but preponderately from American literature. Nothing of epic-making importance apparently appeared during this period. The Editor has obtained interesting comment on many of the articles abstracted from physicians with a special interest in the subject. In some instances the tail seems to wag the dog.

Office Procedures. Paul Williamson, M.D., Philadelphia, 1955, W. B. Saunders Co., 412 pages.

An atlas-sized text which attempts to present instructions for carrying out minor office procedures in a relatively simple way. There are thirty pages in the "pediatric" section. We hope this section is not indicative of the quality of the rest of the book. The author has seen fit to include such topics as poliomyelitis and pancreatic fibrosis. Not only can their inclusion in a text on office procedure be questioned, but the brief comments made are quite without value.

Mental Hygiene in Public Health. Paul V. Lemkau, M.D., New York, 1955, McGraw-Hill Book Company, 486 pages. Price $8.00.

A second edition of the text by the professor of public health administration in the Johns Hopkins School of Hygiene. The author has rewritten the book to keep it abreast of the many developments in mental hygiene that have taken place in mental hygiene since the first edition in 1949.

The Personality of the Young Child. Margaret A. Ribble, M.D., New York, 1955, Columbia University Press, 126 pages. Price $2.75.

A presentation of present-day psychologic concepts written for parents.

A Tiny Baby for You. Nancy Langstaff and Suzanne Szasz, New York, Harcourt, Brace and Company. Price $2.50.

A small book of photographs of infants. About the most useless and pointless book that can be imagined.

Le diabète infantile et juvénile. Pierre Uhry and Paul Ducas, Paris, 1955, Masson et Cie, 487 pages. Price 3,200 fr.

An extensive discussion of the pathology metabolism, symptomatology, and treatment of diabetes in children.

Congresos de pediatria de montevideo. Vol. II. Montevideo, 1954, 551 pages.

Proceedings of the pediatric congress in December, 1951. This was a joint meeting of the III Pan-American Congress and the III South American Congress.

Splenin A in Rheumatic Fever. A. F. Coburn, M.D., L. V. Moore, M.D., J. Wood, M.D., and M. Roberts, M.D., Springfield, Ill., 1955, Charles C Thomas, 87 pages. Price $3.75.

A report on the use of splenin A in the treatment of rheumatic fever.

Editor's Column

THE EVOLUTION OF HEALTH SERVICES IN THE SCHOOLS

MEDICAL inspection of school children in the United States goes back to 1894 when physicians were sent into the Boston schools in an effort to check an epidemic of diphtheria. The years immediately following saw a rapid development of school health services in the larger cities. The chief purpose at this time was the control of the communicable diseases.

Around 1910, with the growth of the child health movement, a new concept of health service in the schools began to prevail. Would it not be possible by giving an annual medical examination to every child to find and correct the defects which handicapped the child's progress in school? This idealistic program was taken up with enthusiasm, but soon ran into trouble. It did not take long to find that an annual examination for every child was an impossible task. The question moreover arose as to just what was to be recorded as a "defect." No standards were available, and no two physicians could agree on the defects in the same child. Further, it was soon realized that the tremendous effort involved was rather fruitless, as facilities usually were not available to correct the defects once they were found. The examinations became somewhat of a gesture and an unused mass of paper records.

As a result, two measures came into use to make the health program more realistic. One was to examine the children several times during their school life rather than annually. By 1925 we find the Parent-Teachers Association putting on a campaign for a "preschool round-up" to find defects before the child entered school. The other suggested plan was "screening" by which the children most likely to have serious handicapping defects could be sorted out for thorough study. The first screening method was the use of height-weight compared against an average, and an extensive campaign was put on to have each child weighed every month at school. The Baldwin-Wood age-height-weight tables came into widespread use. The theory was that the lowest percentile third or fourth would contain nearly all the children with important defects, and in this way they could be screened out for a medical examination. The value of age-height-weight measurements gave ground as the importance of the individual channel pattern of growth became recognized. By 1930 the Third White House Conference on Health Services in the Schools stated that "weight is no longer considered a dependable index of health." However, it was apparently unwilling to discard a procedure whose importance had been drummed into parents and school authorities by years of campaign, as the report went on to say "the weight

of each child should be recorded monthly."

In recent years there have been several studies evaluating screening, or case-finding, methods in the schools. One of the first of these was the Astoria Demonstration Study in New York. Its report was critical of the value of medical examinations as they were being carried out in the schools. Yankauer and Lawrence[1] have reported on a study being made in Rochester, New York. A careful and thorough physical examination was given to 15 per cent of the first-grade school children. All but fifty-nine of 1,056 children examined had received a prior school entrance examination by their private physician or the school health service. Only twenty-one had conditions neither known nor under care, and these were minor. The conclusion was reached that the school medical examination of first-grade pupils who had been examined previously was without value from a case-finding standpoint. Incidentally, they noted that children whose preschool examination had been made by the family physician were more likely to be receiving care than those who had been examined by a school physician.

Recently Davens,[2] of the Maryland State Department of Health, has reported on the school health program in Maryland in which emphasis is being placed on teacher observation and teacher-nurse consultation in screening school children for a thorough medical examination by the physician. The contention is that "the classroom teacher is the only person in the public service who maintains complete and continuous contact with children," and thus "can pick out very nearly all children with significant deviations from physical, mental, and social well being." The teachers are supplied with a guide, *Teacher Observation of Pupil's Health*, on which they can "from time to time, record their impressions for discussion with the nurse." Data from the routine visual and hearing tests are recorded with the teacher's impressions on the child's school health record. Thus the teacher, after consultation with the nurse, screens out the children for medical examination. The importance of the teacher in the school health program is not a new concept, but rather the Maryland plan gives her a place of primary importance in case finding. In a demonstration being carried out in one county the results of this method of screening are stated to be "very encouraging."

The use of the teacher in this way in the school health service brings up a very practical question. Today there is a marked shortage of teachers, and the classroom load in most communities is exceedingly heavy, and seemingly will continue to be for a number of years. In some communities plans are being developed by the school authorities to give the teacher clerical help to relieve her of part of the excessive load now being carried, and to enable her to give more time to teaching, which is her primary function. The question naturally arises whether the teacher can take on this added load of detailed health observation as a basis of screening as outlined in the Maryland plan.

REFERENCES

1. Am. J. Pub. Health 45: 71, 1955.
2. J. Chronic Dis. 2: 409, 1955.